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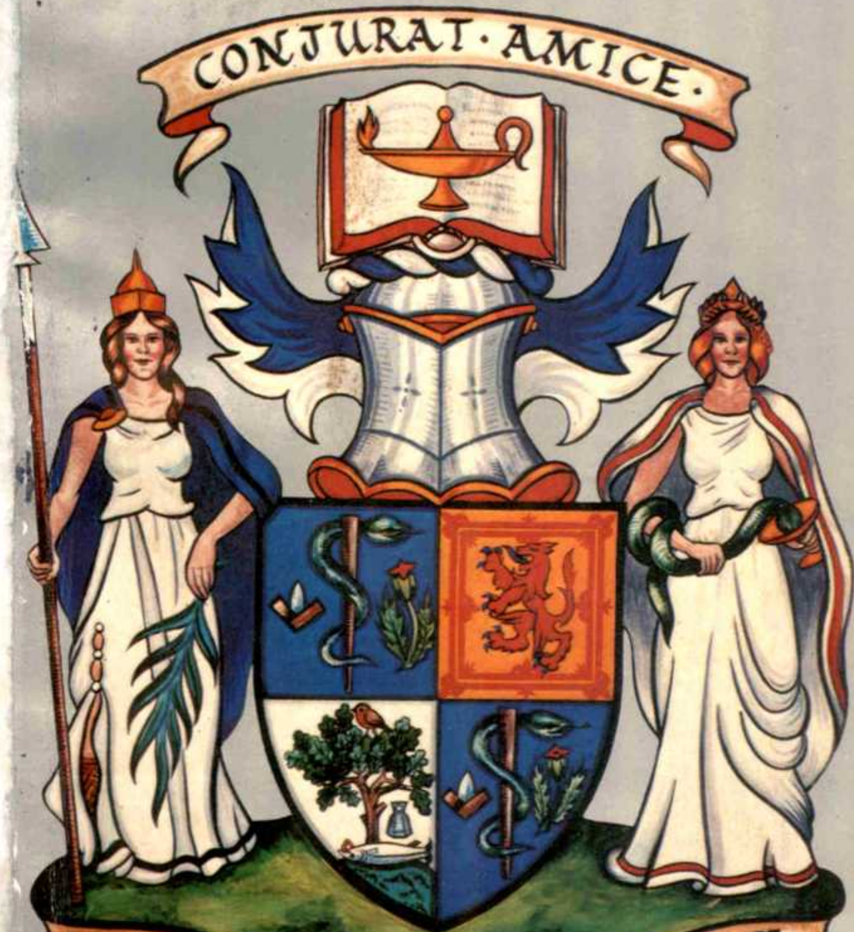
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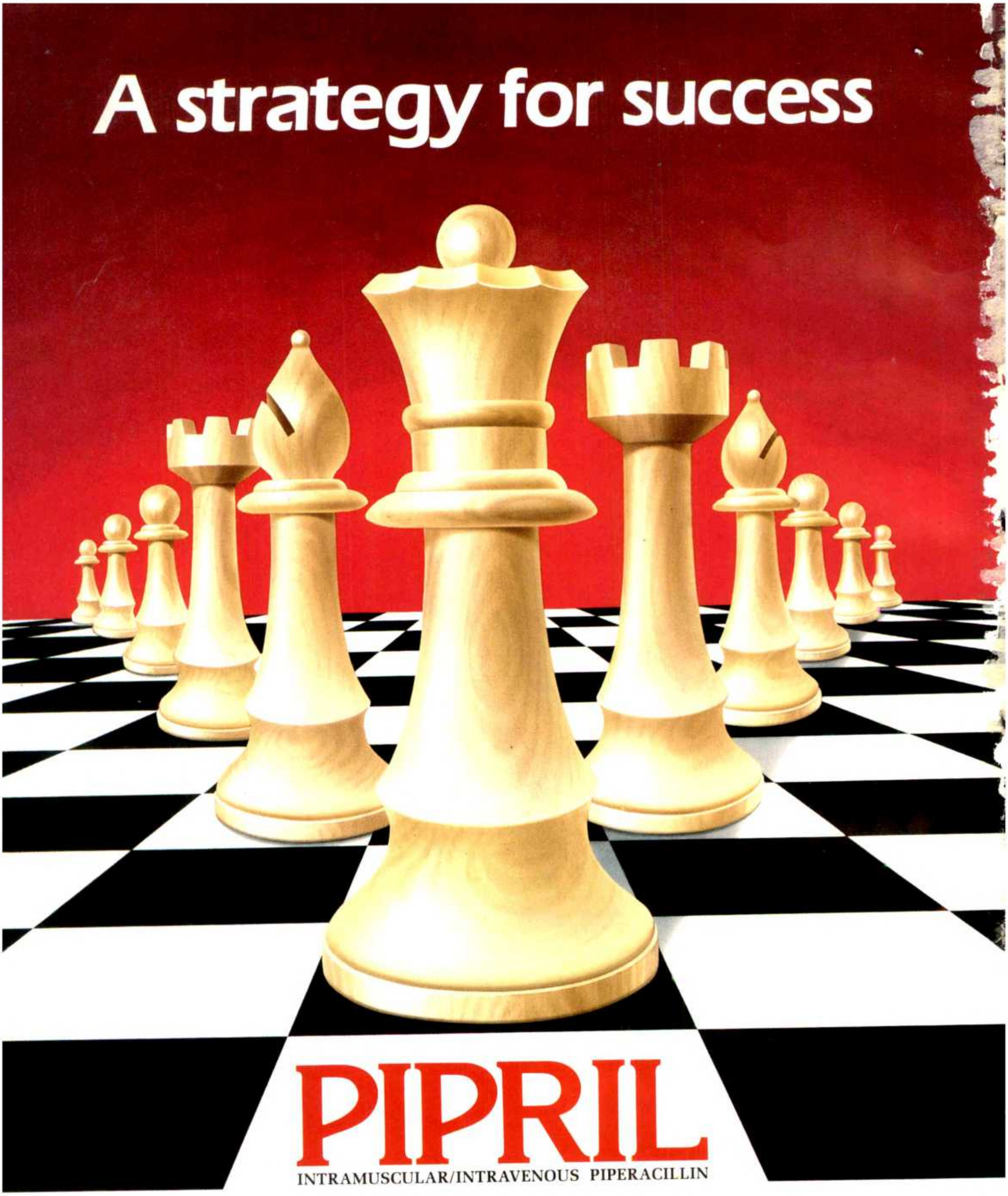

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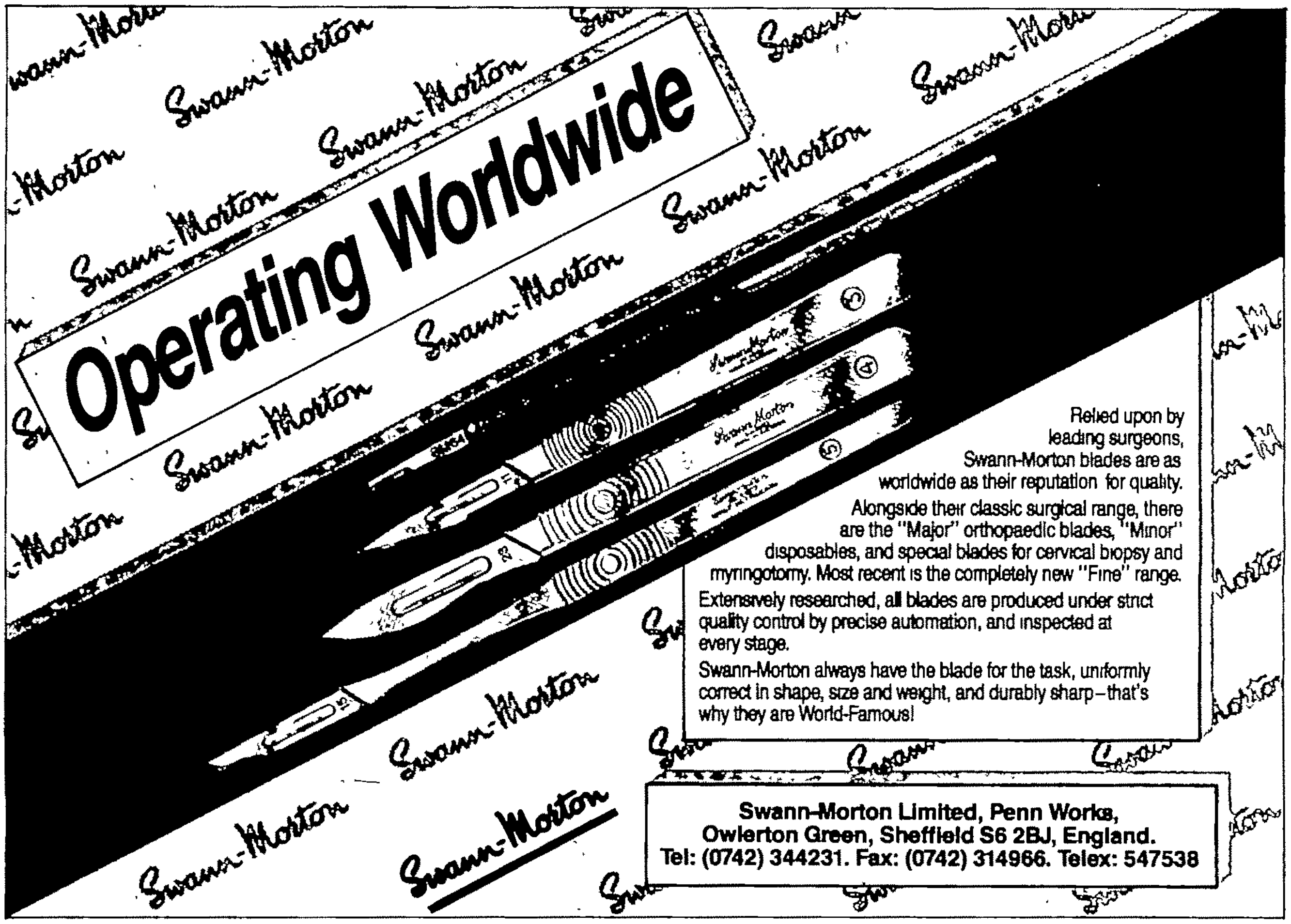

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Readers may be surprised to find in this issue of *The British Journal of Surgery* a recent paper from the prestigious American journal *Surgery*, which is published in full in the format employed by *Surgery*. We have printed this paper as part of a joint experiment between *Surgery* and *The British Journal of Surgery*, to publish one paper from each other's journal for nine issues out of twelve in the next year, after which we will reassess the success of the venture. The Editorial Boards of *Surgery* and *The British Journal of Surgery* decided upon this policy to encourage the subscribers to both journals to investigate the contents of the other journal, and thereby promote both journals. The officers of *The British Journal of Surgery* feel that important work published in UK and European journals is inadequately reviewed by authors in the USA and they hope that this small step may have some effect in encouraging more personal subscriptions in the USA and wider reference to papers published from abroad. *The British Journal of Surgery* has expanded considerably over the last few years; it is now published in India, and the Spanish edition, published in Spanish and marketed in Spain and South America, appeared for the first time in January. We hope that this sample of the excellent material published in *Surgery* will interest our increased international readership.

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Crawford Jamieson

The Chairman
The British Journal of Surgery

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Br. J. Surg. 1989, Vol. 76, July, 660–662

Ductal carcinoma in situ: a new clinical problem

Ductal carcinoma *in situ*, or as it is alternatively known intraduct carcinoma, is now accepted by pathologists as a preinvasive form of breast cancer. It is characterized by a proliferation of transformed and therefore malignant breast epithelial cells, entirely confined to the ducts and without invasion through the basement membrane into the stroma. Some lesions, although predominantly ductal carcinoma *in situ*, have a degree of 'microinvasion' and these tumours should be managed as invasive cancer. This article is concerned entirely with the management of the preinvasive tumours which, for two reasons, has recently developed as a significant clinical problem. Until the 1980s ductal carcinoma *in situ* was an uncommon pathological finding in women presenting with symptomatic breast lumps and was usually treated by mastectomy. This situation has been changed by the introduction of mammographic screening of asymptomatic women and the development and widespread acceptance of breast conserving treatment for cancer.

Breast screening centres such as that at Guildford, UK have seen a threefold to fourfold rise in the incidence of ductal carcinoma *in situ* which now makes up 12–15 per cent of screen-detected cancers[1]. Other units have reported ductal carcinoma *in situ* in as many as 44 per cent of their screen-detected cancers[2]. The introduction of breast screening in the UK will obviously result in a substantial increase in the number of intraduct carcinomas diagnosed, but there is a lack of information to guide the surgeon in their management. What little is known of the natural history of these lesions comes from retrospective reviews, and the results of treatment are almost all confined to anecdotal accounts based predominantly on patients presenting with palpable tumours and not the mammographically detected lesions that are becoming part of our clinical practice. Failure to treat screen-detected ductal carcinoma *in situ* adequately could possibly prejudice the effectiveness of breast screening programmes. It is of major concern that in implementing the Forrest Report little attention has been paid to the problems of treating preinvasive disease and an opportunity seems to have been lost to set up truly national studies and trials to resolve the unanswered questions.

The question that lies at the heart of these problems is that of the malignant potential of ductal carcinoma *in situ*. Evidence regarding the biological behaviour is limited as most cases in the past have been treated by mastectomy and we have to extrapolate from more indirect information. Two studies which reviewed a large number of benign breast biopsies, performed mainly for cystic disease, have identified cases of ductal carcinoma *in situ* previously misdiagnosed and treated only by excision biopsy[3,4]. Both studies found a similar incidence of invasive cancer (27–28 per cent) in the ipsilateral breast, usually in the same quadrant as the original biopsy. The mean time to detection of these invasive cancers ranged from 6·1 to 9·7 years. As these were retrospective studies some important details regarding follow-up and adequacy of excision were not available, but the studies indicate that a woman with ductal carcinoma *in situ* treated by excision alone has a substantial risk, around 11 times that of the general population, of developing an invasive cancer.

Post-mortem studies indicate that the incidence of ductal carcinoma *in situ* in normal breasts is low, around 5–6 per cent, but the disease may be present in up to 40 per cent of mastectomy specimens in association with invasive cancer. In studies where bilateral mastectomy has been undertaken for unilateral breast cancer, ductal carcinoma *in situ* has been found in the contralateral asymptomatic breast, in as many as 60 per cent of cases in one study[5]. Such figures are far greater than the reported incidence of multiple cancers in the same breast (0·1 per cent) and of bilateral breast cancer (4–10 per cent)[6]. These observations support the conclusion from the retrospective review of benign biopsies that not all ductal carcinoma *in situ* (especially the clinically silent cases) progress to the invasive form. However, the question of identification of which lesions remain static or become invasive remains unanswered.

Intraduct carcinomas can be categorized histologically into comedo, cribriform, papillary, solid and micropapillary types. Comedo and papillary forms are the most common and both are associated with multicentric disease; comedo is most likely to contain microinvasive elements[7] and is therefore the most biologically aggressive. Our group[8] has recently observed that the cellular DNA content of ductal carcinoma *in situ* is associated with prognosis. Aneuploid tumours more commonly had foci

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of microinvasion and all patients who had local recurrence had aneuploid primary cancers. Less clear is the expression of the new proto-oncogene (C-erbB.2) which in invasive disease is amplified in approximately 15 per cent of tumours; these patients have been observed to have a poor clinical outcome. In a study of 45 clinical *in situ* tumours 19 (42 per cent) were found to over-express *neu*, and all of these were of the comedo type[9]. Further evidence for the more aggressive biological behaviour of comedo ductal carcinoma *in situ* comes from thymidine labelling studies which reported a significantly higher cellular proliferation rate in this type compared with other forms of intraduct cancer[10].

The clinical dilemma is apparent. How should a lesion of such uncertain natural history be treated? Theoretically, mastectomy will cure ductal carcinoma *in situ* and this is confirmed by a review of the literature. Of 323 cases of intraduct cancer treated by mastectomy and followed for a minimum of 5 years, there was a 1 per cent local recurrence rate and an overall survival rate of 98 per cent. With the adoption of conservation therapy, what should our approach be to a non-malignant tumour in which there is retrospective evidence of a 30 per cent recurrence rate when it is treated by excision alone[3,4]? Two prospective studies of excision alone, one for mammographically detected tumours and the other for palpable ductal carcinoma *in situ*, gave local recurrence rates of 8·5 and 22·7 percent respectively[11,12]. However, these trials were small, comprising only 93 patients and, more importantly, the mean follow-up period was only just over 3 years; a much higher local recurrence rate would be expected with time. Mastectomy could therefore represent over-treatment for many patients with ductal carcinoma *in situ* but in others lesser treatments may jeopardize the chance of cure.

Still to be defined is the effectiveness of adjuvant radiotherapy following excision biopsy, and this is the subject of a number of prospective trials in Europe and the USA. There are some uncontrolled data which suggest that radiotherapy does have an effect. In the National Surgical Adjuvant Breast Project[12], mastectomy was compared with excision biopsy with and without radiotherapy for invasive cancer. Of the 2072 cases recorded, 78 have been reclassified as ductal carcinoma *in situ*. In the 22 patients who underwent excision biopsy the local recurrence rate was 22·7 per cent but fell to 6·9 per cent (with no systemic failures) in the 29 patients who had excision and radiotherapy. A review of other studies confined to the role of radiotherapy after the excision of a palpable mass gives an overall local recurrence rate of 6·3 per cent in 150 patients with a 99 per cent survival rate, although yet again follow-up is too short to see the maximal number of recurrences.

Another problem associated with conservation therapy is that of multifocal disease referred to above. This is normally detected mammographically as widespread microcalcification, although studies on mastectomy specimens have revealed a high incidence of ductal carcinoma *in situ* whether or not it is radiologically determinable. The significance of this is difficult to determine, but it appears from the studies of Page *et al.*[3] that at least 30 per cent of such patients will be expected to develop local recurrence and half of these will be invasive cancer. It would seem logical, until more definite data have accrued from prospective trials, that those patients with widespread microcalcification and biopsy-proven ductal carcinoma *in situ* should be considered for mastectomy.The significance of residual disease following excision biopsy is probably similar. Although our own studies indicate that incomplete excision does not carry a higher recurrence rate than apparent complete excision, in practice we would recommend rebiopsy and, if residual disease is still present, mastectomy.

Failure to take part in clinical studies of invasive breast cancer and the inexplicable habit of clinicians of ignoring the results of these trials have resulted in a situation where a patient with breast cancer may receive treatment varying from radical mastectomy to lumpectomy, the decision often being made on personal prejudice. If we are not to repeat the same mistakes with ductal carcinoma *in situ* then we need the co-operation of trials organizations such as those funded by the Medical Research Council and Cancer Research Campaign to implement studies in which all breast screening centres should co-operate.

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Review

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Technical aspects of war wound excision

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Excision of war wounds may be performed by civilian surgeons with no previous experience of war surgery. The principles of complete excision of non-viable tissue with removal of foreign material, leaving the wound open, and delayed primary closure of skin are vitally important. A major part of the surgical approach is wound assessment and the formation of an operative plan. The extent and ease of the operation depends on the site, age and type of wound. Attention to the technique of wound excision avoids septic complications and permits skin closure when the first dressing is removed. Wounds may need re-excision at a later date. Modification of surgical management is necessary when certain difficult areas are wounded and when the patient presents after many days or has suffered inappropriate first aid.

Keywords: War, wounds and injuries, débridement

The International Committee of the Red Cross (ICRC) has surgical hospitals for war wounded in six countries. The two largest are in Pakistan and Thailand for the wounded from the Afghan and Cambodian conflicts respectively. The hospitals depend on surgical teams from the National Red Cross Societies of many countries. Most of the surgeons are drawn from civilian practice and a mission with ICRC represents their only exposure to war wounds.

War surgery literature stresses the necessity of complete wound excision (débridement)[1,2]. That this is an easy surgical exercise is an assumption. In reality the operation is frequently performed inadequately. Excision of extensive wounds from, for example, a land mine is neither quick nor easy. Attention to the technique of wound excision reduces the number of operations, shortens hospitalization and in some cases saves lives and limbs. After resuscitation, the highest priorities are soft tissue healing and delayed skin closure which will not be achieved if the wound is not adequately excised. The efficiency of a field hospital is directly related to the adequacy of the wound excisions performed.

The ICRC has produced a film entitled *War surgery: an introduction*[3]. It shows real wounds, their excision and other aspects of wound treatment. It also shows the consequences of missing devitalized muscle at the time of wound excision. It stresses the basic and important principles of: excision of all non-viable tissue and foreign material, leaving the wound open, and delayed primary closure of skin.

For geographical and political reasons the ICRC hospitals are situated some distance from the battlefield. This results in some of the wounded presenting after days or weeks. The surgical management must be flexible to take into account the wound changes this delay produces.

Preoperative considerations

The wounded patient

A systematic clinical assessment of the wounded patient is essential. Important historical points are the type of weapon and the time since injury. Examination should detect signs of serious injury from penetrating missiles such as surgical emphysema around chest wounds. A full assessment of the wound may not be possible until plain radiographs have been taken and the patient is in the operating theatre and under anaesthesia.

The patient is resuscitated with intravenous fluids and cross-matched blood as appropriate. Patients seriously wounded more than 24 h before admission are usually anaemic and dehydrated but haemodynamically stable. Such patients rarely have to go to surgery immediately.

All patients with open wounds admitted to an ICRC hospital receive 5×10^6 units of benzyl penicillin, antitetanus serum and a course of tetanus toxoid.

Preoperative radiography

Plain radiography is a valuable part of wound assessment. The presence of a fracture changes the operative plan and post-operative care. Radiographs help to determine whether a severely injured limb can be salvaged or not.

Metallic foreign material indicates the nature of the weapon and the depth of penetration. The patient may not know how he was wounded. The absence of metallic material usually indicates a through and through wound. This should lead the surgeon to look for an inconspicuous entry wound. Alternatively, foreign material may not be radio-opaque. Pieces of shoe and mud are commonly present in wounds from antipersonnel mines and are particularly dangerous. Some such weapons have plastic fragments. The absence of metallic material does not indicate a less severe injury.

The radiographic presence of gas in the tissues does not necessarily indicate clostridial myositis which is obvious clinically and at operation. High velocity missiles are associated with palpable and radiographic intrafascial gas in healthy tissue some distance from the wound (*Figure 1*).

Anaesthetic considerations for the surgeon

The anaesthesia involved in the surgery of war wounds may be complex and demanding especially with wounds of the head, neck and chest. The extensive use of ketamine by ICRC anaesthetists is well recorded and is associated with few unpleasant side effects[4]. This is a safe anaesthetic agent and can be given to a hypovolaemic patient. The surgeon must be aware that it will make a normovolaemic patient hypertensive and that movement and phonation are not uncommon. Spinal anaesthesia for lower limb injuries is ideal, giving good operative conditions with hypotension.

It is essential that the surgeon and anaesthetist discuss the type of anaesthesia to be used, the position of the patient and the order of operation for multiple wounds. The surgeon must indicate the likelihood of a longer procedure, such as laparotomy or vascular repair, being needed.

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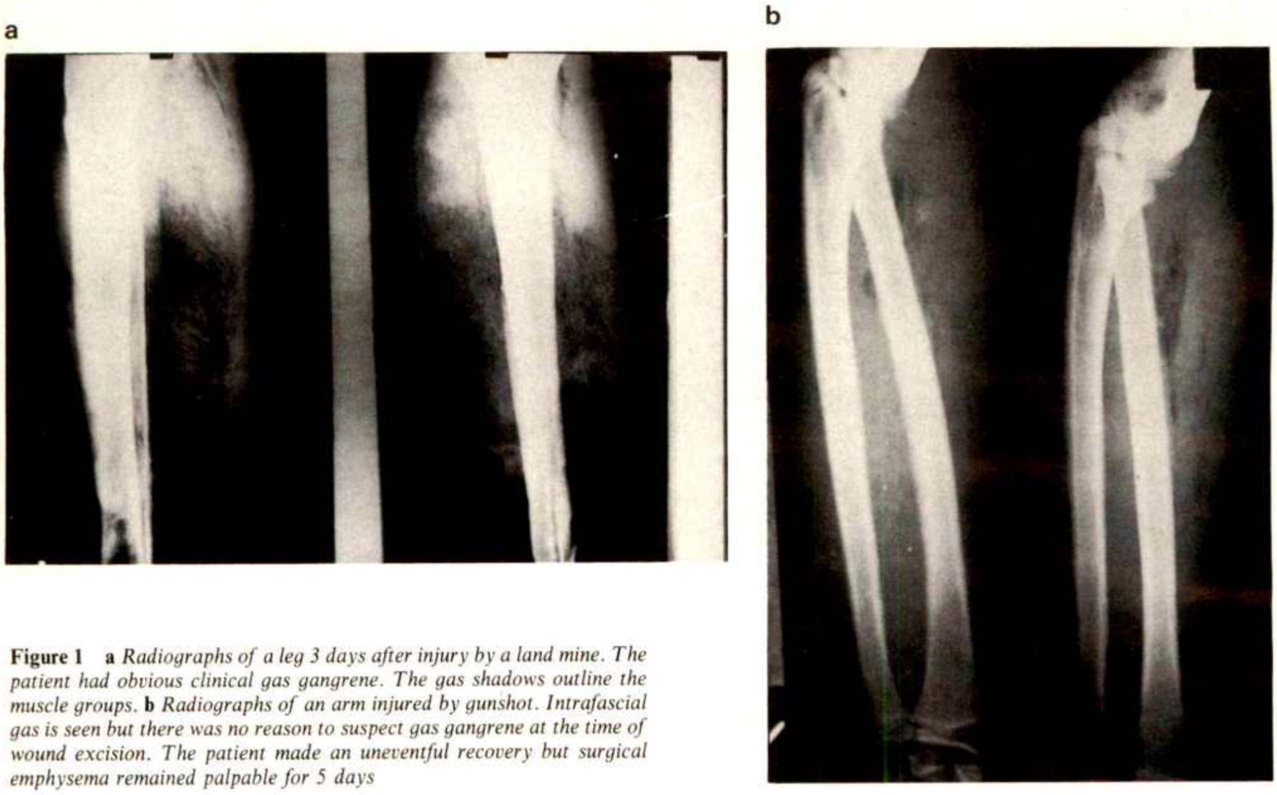

Figure 1 **a** *Radiographs of a leg 3 days after injury by a land mine. The patient had obvious clinical gas gangrene. The gas shadows outline the muscle groups.* **b** *Radiographs of an arm injured by gunshot. Intrafascial gas is seen but there was no reason to suspect gas gangrene at the time of wound excision. The patient made an uneventful recovery but surgical emphysema remained palpable for 5 days*

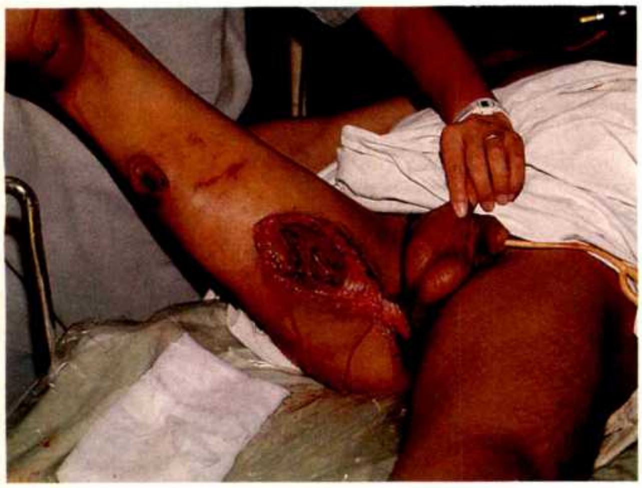

Figure 2 *Photograph of an injury of the right thigh. The entry wound, unseen, is high on the left buttock. The missile passed across the pelvis and made an exit between the anus and scrotum. It then entered the patient's right thigh (larger wound) and made its second exit slightly lower (smaller wound)*

Operative planning

When the patient is under anaesthesia a wound assessment is made by examination of the injured area or limb. The operation is planned accordingly. It is easy to miss a small wound which is the entry point of a high velocity missile. Such missiles can take long and surprising routes through the body (*Figure 2*).

Most wounds can be thought of as a cavity containing dead tissue which, with its skin margins, must be excised back to healthy tissue. Bearing in mind the mechanism of injury facilitates this concept.

Having assessed the wound the surgeon can predict the nature and extent of the operation. As a general rule the most severe injury possible should be expected as it is frequently encountered. For example, a missile which has penetrated the buttock should be expected to have entered the pelvis injuring rectum or bladder.

Limbs are involved in 73 per cent of war wounds[5]. A pneumatic tourniquet is invaluable in the initial surgery of distal limb wounds. Its application before removal of field dressing minimizes blood loss. The bloodless operative field then facilitates wound excision.

Wound excision

Operative technique

A basic set of instruments for wound excision includes a scalpel, large curved scissors, toothed dissection forceps, a curette, six haemostats and two medium-sized, lipped retractors. Diathermy is not necessary. Ligature material should be absorbable.

The skin is prepared with an antiseptic solution and the operative field draped in accordance with the operative plan. Drapes with holes should only be used for the smallest and most superficial wounds. The surgical wound is always larger than the initial wound.

As little skin as possible is removed. It is resilient tissue. Only that which is non-viable around the wound edges is excised. The wound can be enlarged further by appropriate incisions. Limb incisions should be longitudinal which allows decompression of viable muscle and easier visualization of damaged structures.

A thorough wound excision involves display of all structures in the wound 'cavity'. Individual muscles and tendons are dissected bluntly and their damaged part excised back to healthy tissue. Viable muscle is recognized by its colour, bleeding, texture and contractility. Heavily blood-stained and contaminated intermuscular fascia is excised. With through and through wounds the skin incisions and dissection are based on both entry and exit wounds (*Figure 3*) and if possible should meet. The exit wound is usually the larger.

When the wound includes a fracture, that part of the bone must also be displayed. Any small or unattached bone fragments

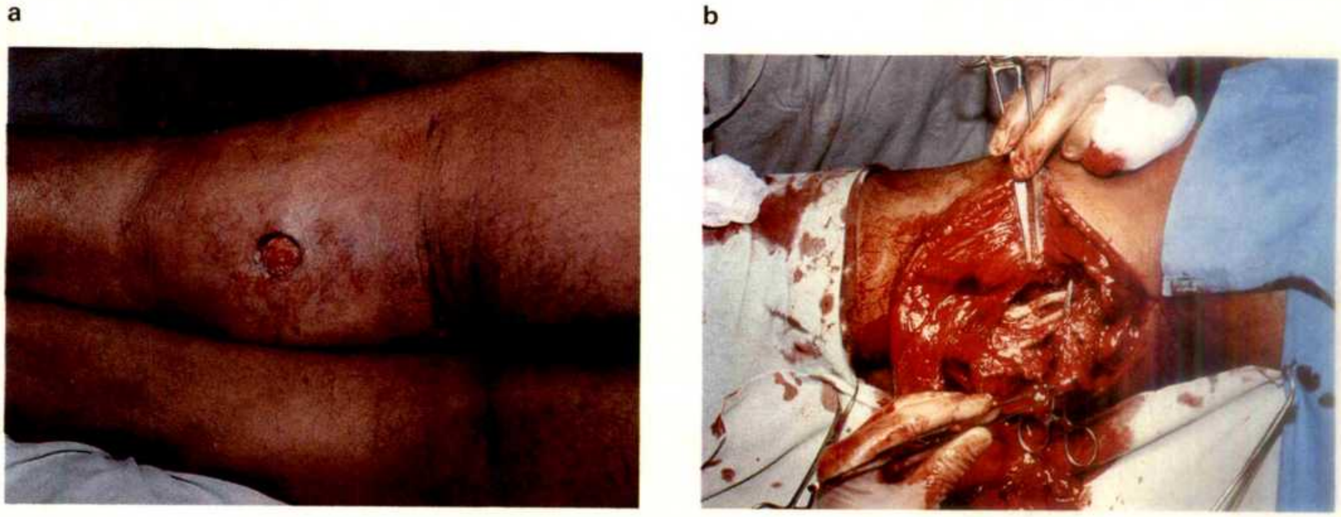

Figure 3 **a** *The posterior aspect of the left thigh and the exit of a gunshot wound 6 days after injury. A swab has been pushed into the wound at the time of injury.* **b** *The same wound in the process of excision. The lateral side of the wound has been excised. Non-viable muscle is still visible on the medial side of the wound*

must be removed. This may ultimately involve removal of a large segment of bone. Curettage of exposed medullary bone back to firm marrow is necessary. Bone left *in situ* is cleaned of dead muscle and foreign material. Unattached fragments left *in situ* act as a nidus for chronic wound infection and will not act as a bone graft. The priority is soft tissue healing.

As much foreign material as possible is removed. Small metallic fragments can be difficult to find and prolonged surgery to find them is unnecessary and dangerous. Only rarely do these cause problems. The foreign materials that must be removed because of their tendency to cause severe wound infection are: mud, pieces of shoe, cloth and extrinsic bone fragments[3,6]. The last of these are blown in from another person or another part of the patient and on radiographs can easily be mistaken for a fracture.

The wound is best judged as having been excised adequately by direct visualization and the surgeon's finger. Foreign material, loose bone fragments and, with experience, devitalized muscle can be felt in the wound depths. One should be able to see and feel that the excision is complete.

Haemostasis is achieved by ligation of vessels with absorbable material and compress application. The wound is liberally washed with saline. Antiseptic solutions at this stage are of no value. They do not excuse leaving dead or contaminated tissue and will not prevent infection of such tissue. The treatment of war wounds is surgical and not chemical.

Sutures for closure are never applied at this stage except to the face, scalp, dura, joint capsules and serous cavities.

The operative dressing is dry gauze, loosely fluffed, in sufficient quantities so that blood and serum will be taken up. Vaseline gauze or antiseptic dressings are not used. Gauze moistened with normal saline may be applied over exposed joints and tendons.

Pitfalls in wound excision

The consequences of missing dead muscle when excising a large wound are disastrous[3]. When a muscle group is injured only those individual muscles which are partially divided are visible in the wound. Those muscles completely transected contract away from the wound. Their devitalized ends must be exposed by adequate skin incisions and dissection.

The advent of the external fixator has facilitated the treatment of large soft tissue wounds associated with limb fractures. Wound excision is hampered by rigid fixation. The application of an exteral fixator has a lower priority than wound excision and so should be delayed until the first dressing 4 or 5 days later. If further wound excision is required it can be more easily performed before the fixation is applied. There is no need to immobilize the limb by means other than a plaster of Paris splint or skeletal traction in the first instance. By this regime external fixation is performed on a routine list and not as an emergency. Moreover the pin sites are theoretically likely to become infected if made when the patient has just been brought in from the field.

The fascial compartments below the knee are prone to the compartment syndrome, particularly the anterolateral compartment. The condition should be expected in any penetrating wound below the knee with or without a tibial fracture. A missile passing through a compartment can cause necrosis of the muscles therein without gross swelling of the limb. Open fasciotomy by incisions on both sides of the leg shows the extent of muscle devitalization and if performed early enough prevents further necrosis. The surgeon should be prepared to perform open fasciotomy at the time of wound excision. The degree of muscle necrosis can necessitate excision of all muscle in the compartment. This is a large wound but heals remarkably quickly (*Figure 4*).

Injuries of nerves and vessels

It is not within the scope of this review to describe the surgical approach to injured nerves and vessels. Attention is drawn to other texts which cover this subject[1,2,7].

Large nerves are resilient. They are often the only structure left running through the wound cavity. Although contused they should be left intact and the wound excised around them. Some recovery may be possible. There is no place for primary nerve repair at the time of wound excision.

When the patient survives injury to major vessels and the periphery is rendered ischaemic the affected limb is rarely salvageable. Reconstruction of vessels across a large wound cavity is difficult and must be covered by viable muscle if it is to succeed. Vascular injuries that can be repaired are usually caused by small fragments from shell or mine with minimal damage to surrounding structures. In an ICRC hospital, because of the delay in presentation most vascular injuries present as gangrenous limbs requiring amputation, pseudoaneurysms or arteriovenous fistulae.

Traumatic amputation

Traumatic amputation is a common injury especially of the foot or lower leg by a land mine. The surgeon must be aware that damaged tissue and earth may be pushed up within the fascial compartments (*Figure 5*). The surgical amputation is at a higher level and may resemble a thorough excision of the original

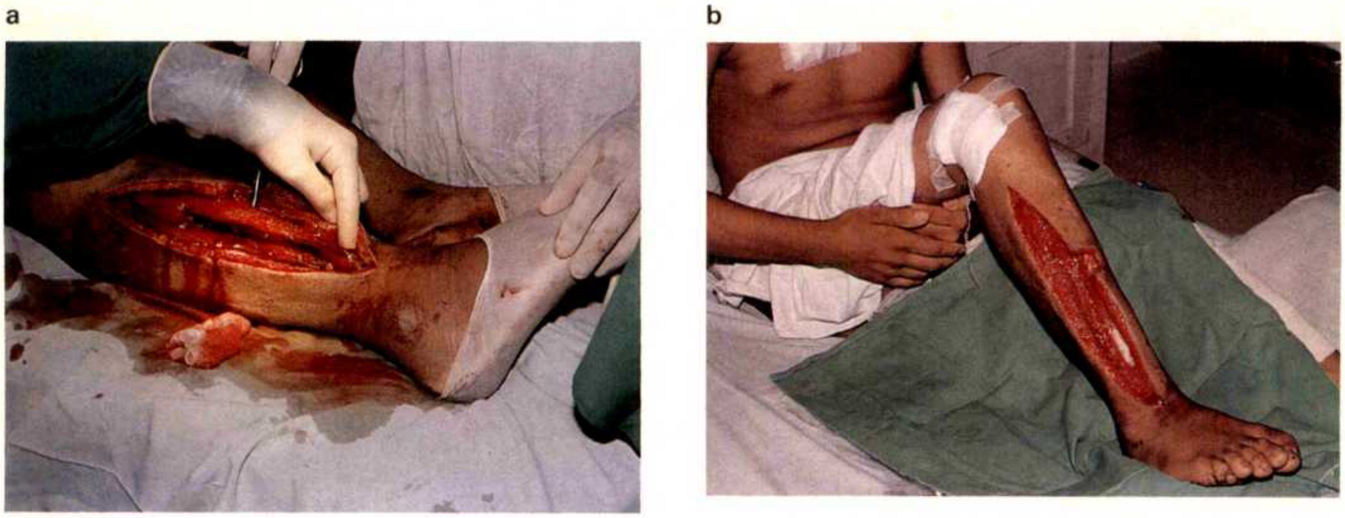

Figure 4 **a** *The lateral aspect of a leg injured by a shell fragment which passed between the tibia and fibula without fracture. The injury was 2 days old. The missile track is indicated by the artery forceps. The surgeon's finger shows necrotic extensor muscle some distance from the wound.* **b** *The wound seen in* Figure 4a *after 7 days of regular dressing and the day before closure by suture and skin graft*

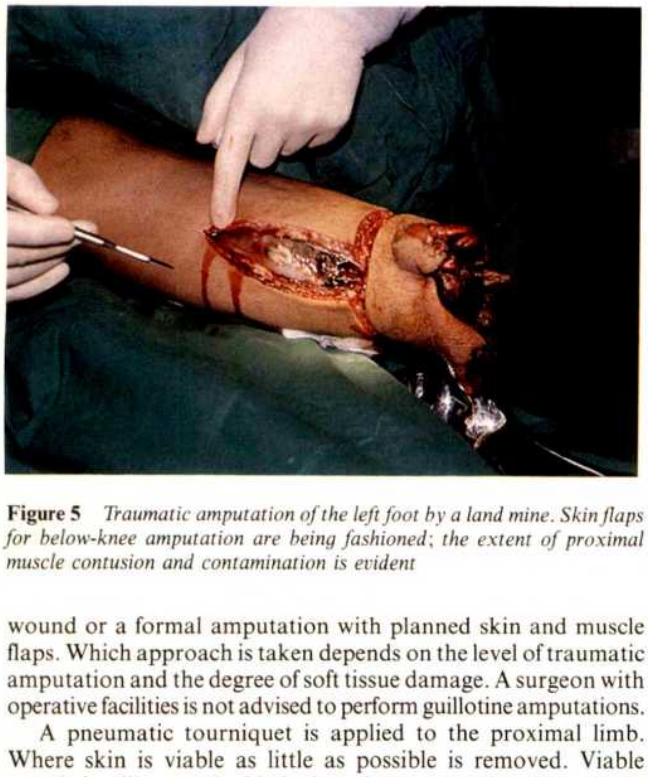

Figure 5 *Traumatic amputation of the left foot by a land mine. Skin flaps for below-knee amputation are being fashioned; the extent of proximal muscle contusion and contamination is evident*

wound or a formal amputation with planned skin and muscle flaps. Which approach is taken depends on the level of traumatic amputation and the degree of soft tissue damage. A surgeon with operative facilities is not advised to perform guillotine amputations.

A pneumatic tourniquet is applied to the proximal limb. Where skin is viable as little as possible is removed. Viable muscle is still recognizable by its colour, texture and contractility in a temporarily ischaemic limb. The bone and muscle sections are made to excise devitalized and contaminated muscle and to permit delayed closure of the remaining skin.

After performing above-knee amputation, release of the thigh tourniquet causes muscle to retract in relation to the bone and skin flaps. This must be remembered when planning the level of skin and muscle section.

It is rare to be able to perform a below-knee amputation with a long posterior myocutaneous flap. The wound is usually such that the soft tissues on the back of the leg must also be excised. Equal skin flaps are usually the sole option.

Principal vessels are transfixed with an absorbable suture. Haemostasis must be achieved after release of the tourniquet.

The surgical amputation is left open, with no sutures applied, and delayed suture is performed after 4 or 5 days when soft tissue can be trimmed. Failure to achieve this is due to the remaining skin being too short in relation to the bone section. In the period between surgical amputation and delayed suture the skin retracts up the stump and the exposed muscle swells. An amputation which looks as though it would close easily at the time of operation may only do so with further trimming of bone and muscle. A suction drain should be placed beneath the skin flaps when the delayed suture is performed.

Re-excision of wounds

Some time after the initial wound excision it may become apparent that this was incomplete. In the early days, temperature, excessive pain and copious purulent discharge into the dressings are indications to return the patient to theatre. The wound is reassessed and any remaining devitalized tissue is excised.

After many days or weeks failure of a wound to heal or visible bone indicate that more soft tissue or bone has to be removed. A degree of healing will have occurred around the wound which remains a cavity containing non-viable tissue, bone fragments or protruding ends of fractured long bones. Access to this cavity may be difficult. The only course is to reincise the skin, curette the cavity and excise dead bone ends with powerful bone nibblers. When the re-excision is complete, digital examination confirms a smooth cavity free of bone ends and fragments. This cavity will slowly heal in by secondary intention and ultimately callus will form across it.

Factors modifying the technique of wound excision

Areas where wound excision is difficult

There are areas of the body which when injured do not lend themselves to wound excision. Aggressive excision of all non-viable tissue from these areas would result in loss of the patient's life or irreversible loss of function of that part. Such areas, in the author's experience, are the neck and parapharyngeal spaces, the retroperitoneum and the pelvis. As in other branches of surgery, the operator must accept that complete excision of some lesions will result in massive blood loss and an irreparable defect. The best that can be achieved is the repair or avoidance of vital structures, haemostasis and, if the patient survives, repeated wound toilet.

Another area of particular difficulty is the tarsus because gaining access to all damaged tissue and bone fragments would involve complete tarsal disruption. Repeated vigorous curettage along the track is recommended.

A penetrating war wound of the abdominal wall is an indication for laparotomy. The wound is rarely a problem in comparison to the visceral damage. The visceral surgery most commonly involves intestinal repair or resection with proximal diversion or exteriorization when the colon is involved. Liver injuries are frequent and usually require suture haemostasis only. After laparotomy the wound itself is excised and if possible the peritoneum is closed. An abdominal wound including a left-sided large bowel injury usually involves that part of the abdominal wall preferred for the stoma. This problem can be overcome by colonic mobilization and bringing out the colostomy in an unconventional site. Colostomy through an abdominal wall wound is not recommended.

Inappropriate first aid

Despite the lessons that have been learnt this century, practitioners of first aid in countries at war continue to suture war wounds primarily. Wounds sutured in the field invariably putrefy and should be completely excised even if the skin has apparently healed[6]. The wound is left open as described above and resutured after 4 or 5 days.

Field tourniquets applied high on a limb many hours or even days before present the surgeon with a dilemma. Should he release the tourniquet, excise the wound and risk renal failure from myoglobinaemia or should he amputate above the tourniquet? A reasonable guideline might be that if there has been complete vascular occlusion for more than 6 hours then he should amputate proximal to the tourniquet.

Old wounds

Many of the injured with whom ICRC is concerned travel for a long time before reaching medical aid. An ICRC surgeon's experience of the effects of modern weaponry differs markedly from that of his military counterpart who receives the wounded soon after injury. This delay necessitates changes from conventional management. The wound may require more aggressive surgery because of putrefaction or gangrene. Alternatively the wound assessment may reveal that the wound has started to heal and so a less aggressive surgical approach may be taken[6].

Operative blood loss when excising an old wound may be great because the surgeon is working through oedematous and inflamed tissues. It can be difficult to identify viable muscle under these circumstances.

The nutritional status, anaemia and dehydration of a patient with putrefied wounds inevitably lead to poor healing after wound excision. This necessitates a longer period before delayed suture.

Dressings

After wound excision the operative dressing is left for 4 or 5 days and removed in the operating theatre with the patient under anaesthesia. When correct wound excision has been performed the muscle adheres to the adjacent gauze and contracts away as the dressing is gently peeled off. The wound is then ready for suture or skin graft. If there is pus or evidence of dead muscle the affected part of the wound must be more widely excised and again left open with gauze dressings.

To leave the dressing undisturbed for 4 or 5 days requires confidence in the initial wound excision. Further confidence is needed when the dressing is soiled and offensive after 2 or 3 days. Providing the patient remains well and apyrexial such a dressing should be left undisturbed until the set date. The state of the dressing is no indicator of the state of the wound especially in a field hospital in a hot country.

At the time of first dressing change a wound is occasionally seen which has a light seropurulent discharge yet all the tissues are viable. This requires further dressing every day or two until clean enough to close. In such a case an antiseptic such as a weak sodium hypochlorite solution may help.

Delay of closure beyond the first dressing change

Closing the wound on the fourth or fifth postoperative day is recommended on the assumption that the patient is a fit young person with a non-infected, completely excised wound. If the wound is not clean or was infected before initial surgery an extended period of dressing may be required before closure. A large wound may need longer before it will accept a split skin graft.

Those patients presenting after several days may need their skin closure delayed further. It is wise to plan this if the patient is anaemic, or his nutritional status is poor. In these circumstances an apparently clean wound, when sutured, can fail to heal.

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Ileitis and pouchitis after colectomy for ulcerative colitis

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Ileitis can occur after surgical treatment of ulcerative colitis. Following continent ileostomy or restorative proctocolectomy ileitis can become a serious clinical problem and is then known as pouchitis although this condition is yet to be clearly defined. It is likely that pouchitis is the result of an abnormal host response to a change in bacterial flora and that the nature of this host response is related to the underlying pathogenesis of ulcerative colitis. Continued study of the immunological basis of ulcerative colitis is therefore required to solve the problem of pouchitis.

Keywords: Ulcerative colitis, surgery

'Pouchitis' is a term coined by Kock *et al.*[1] to describe the reservoir ileitis that occurred in a number of his patients with ulcerative colitis who had undergone the operation of continent ileostomy. He had first reported this procedure[2] in five patients in 1969 and since that time there have been numerous descriptions of pouchitis in the literature.

In 1980 the operation of proctocolectomy with ileal reservoir and anal anastomosis was described by Parks *et al.*[3] and it became clear that this operation, when performed for ulcerative colitis, also produced pouchitis in a number of patients. The aetiology of pouchitis is uncertain but there are a number of situations in which ileitis can occur after surgery for ulcerative colitis.

Ileitis following colectomy and conventional ileostomy

In the 1940s and early 1950s the development of ileitis in the terminal ileum immediately proximal to the ileostomy following the operation of colectomy was recognized as a serious and not uncommon complication of the operation[4]. It was on occasion associated with perforation of the diseased small bowel in the early postoperative period and this complication was initially felt to be due to placing the ileostomy too close to the caecum in the site of preoperative 'backwash' ileitis[4–7]. A type of ileitis was then described[8] which could be relieved by stomal dilatation and lavage with a catheter, and it became widely accepted that postcolectomy ulcerative disease of the ileum was secondary to chronic ileostomy obstruction (dysfunction) and was reversible if the obstruction was removed[8,9].

Since the introduction of the Brooke or Crile–Turnbull techniques of ileal eversion and primary mucocutaneous suture, ileostomy obstruction due to early oedema or late fibrosis has become rare, as has ileitis following colectomy for ulcerative colitis. However, it does still occur[10–12] and usually requires further operation and ileal resection. It may well be that in at least some of these patients this complication is in fact due to the existence of Crohn's disease.

Ileitis in the reservoir of Kock's continent ileostomy

In 1969 Kock described an operation in which an intra-abdominal reservoir and 'continent' ileostomy were constructed[2]. By 1976 he had performed 164 of these operations but had encountered non-specific ileitis in the reservoir of 14 patients. These had all been successfully treated by catheter drainage and sulphasalazine[13] and it was felt that the mucosal inflammation was due to stasis and overgrowth of anaerobic bacteria[1]. Other authors[14] reported that the incidence of this complication varied from 13 to 43 per cent and that it was not a problem in pouches constructed for familial adenomatous polyposis[15]. However, mucosal biopsies of all reservoirs showed histological evidence of inflammation and this was more severe in the ulcerative colitis patients. Clinically, pouchitis causes bloody diarrhoea associated with abdominal cramps and occasionally fever[16]. Most authors agree that conservative treatment is usually successful although removal of the reservoir is sometimes necessary[17].

Other patients sometimes develop troublesome diarrhoea without evidence of mucosal inflammation[18,19] and the incidence of this problem varies from 7·5 to 32 per cent. This clinical picture may be related to a change in bacterial flora and comparison of conventional ileostomy effluent, intra-abdominal reservoir content and normal faeces has shown differences in both the numbers of micro-organisms and the ratio of aerobes to anaerobes[20]. The most frequently isolated anaerobes were *Bacteroides*, clostridia and anaerobic streptococci, and the bacterial constitution of ileostomy reservoir content seems to hold an intermediate position between conventional ileostomy effluent and normal faeces. Micro-organisms are known to be potent producers of metabolites and toxins which could lead to changes in the ileostomy reservoir, and by consuming essential substances from the intestinal contents the bacteria could possibly impair absorption[20].

Other studies have indeed shown that vitamin B_{12} absorption is reduced in patients with a continent ileostomy when compared with those with a conventional ileostomy[21]. Steatorrhoea was also reported, and in four of seven patients with a continent ileostomy there was evidence of a stagnant loop syndrome as oral lincomycin treatment resulted in increased absorption of B_{12}, decreased excretion of faecal fat and decreased concentrations of *Bacteroides* in the ileum[21]. Changes in the amount and composition of bile salts in the ileostomy reservoir have also been reported[22].

Certain morphological changes appear to take place in the mucosa of an ileostomy reservoir[23]. There is a decrease in villus height but an increase in the number of crypt cells and mucosal

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volume. During the first year after operation the epithelial turnover increases, but after 6–10 years turnover seems to normalize In this study there were no signs of alarming changes such as dysplasia or progressive atrophy, and the morphological changes may represent adaptation of the mucosa to the change in luminal bacterial content.

Ileitis in the ileal reservoir following restorative proctocolectomy

The desire to avoid a permanent ileostomy in patients requiring surgery for ulcerative colitis or familial adenomatous polyposis has led to the development of the operation of restorative proctocolectomy. This was initially described in experimental models both with[24] and without[25] an ileal reservoir Parks *et al.*[3] reported the clinical results of proctocolectomy with ileal reservoir and anal anastomosis in 1980, and it is now well established that the addition of an ileal reservoir produces better results than a straight ileoanal anastomosis[26,27]

The commonest complications of the procedure include intestinal obstruction, pelvic sepsis, anastomotic dehiscence and stenosis However, inflammation in the reservoir is common, although most cases are subclinical in fact, chronic inflammation has been found in up to 90 per cent of patients[28]. Pouchitis is characterized by acute inflammation with endoscopic changes and frequent, loose stool and occurs in between 8 per cent[29] and 20 per cent[30] of patients. Its occurrence does not appear to be related to the type of reservoir or the residual volume, suggesting that stasis is not a major factor, but it is much commoner in those patients with a diagnosis of ulcerative colitis.

The faecal flora of pouches contains a greater predominance of anaerobes and increased numbers of *Bacteroides* compared with the faecal flora of ileostomies[31], and similar histological changes have been demonstrated in pouches as occur in Kock's intra-abdominal reservoirs[32]. Although in some cases pouchitis is a very serious complication, occasionally requiring removal of the pouch, most authors still agree that episodes of pouch inflammation are usually successfully treated with metronidazole[33,34]. The usefulness of metronidazole in this context may be because of its immunosuppressive[35] rather than its antibacterial activity, but is of interest as the drug does not appear to have a role in the treatment of ulcerative colitis[36].

In conclusion, it is therefore apparent that non-specific ileitis can occur after colectomy for ulcerative colitis whether a conventional ileostomy, continent ileostomy or pouch operation is performed. As this does not occur after surgery for familial adenomatous polyposis, it is likely that the aetiology of reservoir ileitis or pouchitis is related to the aetiology and pathogenesis of ulcerative colitis rather than any purely mechanical effect of the reservoir itself.

Although the changes in bacterial flora may be secondary to stasis and themselves give rise to the histological changes in the mucosa, the problem of pouchitis is not just a histological phenomenon and is unlikely to be solved until the pathogenesis of ulcerative colitis itself has been more fully elucidated.

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Tumour necrosis factor and bacterial sepsis

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This review examines the evidence that tumour necrosis factor is the principal mediator of the derangements associated with severe sepsis.

Keywords: Cytokines, bacterial sepsis

Sepsis in surgical patients is associated with a constellation of responses which include fever, hypotension, tachycardia, anorexia, fluid retention, electrolyte abnormalities and hyperglycaemia. If the infection is prolonged, anorexia and increased breakdown of adipose and lean tissue occurs, and these alterations may progress to single or multiorgan failure. In the past these host responses to infection have been attributed directly to the effects of toxins from invading bacteria or to the presence of widespread tissue destruction However, it is now recognized that the host itself generates signals that result in these adverse responses[1,2]

There is now increasing evidence that the primary afferent signal generated by the host that leads to many of the changes associated with life-threatening sepsis is the cytokine tumour necrosis factor (TNF/cachectin), a 17 000 molecular weight polypeptide produced by stimulated reticuloendothelial cells, principally macrophages and monocytes[3]. This cytokine was named tumour necrosis factor because of the history of its isolation and characterization At the end of the last century, William Coley, a New York surgeon, demonstrated that the injection of certain bacterial products locally into oropharyngeal tumour sites induced tumour regression[4]. In 1975 Carswell *et al.* demonstrated that a soluble factor released by the host after exposure to bacterial endotoxins was responsible for tumour cytotoxicity, and this factor was termed tumour necrosis factor[5]. Only when the amino acid sequence of the molecule was determined was it realized that this substance was identical to cachectin, a newly discovered macrophage product, which was believed to cause adverse host responses to bacterial invasion.

The purpose of this review is to examine the evidence supporting the hypothesis that TNF is a principal host mediator of the derangements associated with severe sepsis.

To demonstrate a cause–effect relationship between a molecule and any putative effects it may have *in vivo* requires that a series of experiments be performed to answer specific questions, similar to those posed by Koch who was faced with the same difficulties when attempting to prove the association between micro-organisms and disease[6]. The first requirement for such a proposal is that the molecule can be demonstrated in the circulation at the time when host responses are initiated. Early attempts to demonstrate the presence of circulating TNF gave inconsistent results in that TNF was not generally detected in the plasma of patients with established sepsis[7]. A major exception to this was the finding that circulating TNF was almost invariably demonstrated in the plasma of patients dying of meningococcal septicaemia[8,9]. These observations led to the suggestion that TNF might be released as a single pulse, following an appropriate provocative stimulus, to produce biological effects that far outlive its survival at detectable levels in the bloodstream. Thus, by the time that symptoms become established the molecule has already initiated the responses and is no longer detectable by conventional techniques.

This hypothesis has been tested in baboons receiving lethal injections of live *Escherichia coli* organisms. TNF was always present in the circulation at the onset of shock but disappeared from the circulation several hours before death[10]. The pulsatile nature of TNF release has been confirmed in studies involving healthy humans receiving bolus intravenous injection of *E. coli* endotoxin. TNF was present in the circulation 90–180 min after endotoxin administration and its first appearance was associated in time with the onset of symptoms, fever, tachycardia and neurohormonal responses. Furthermore, the magnitude of TNF-release following a standard dose of endotoxin predicted the extent and duration of the ensuing clinical and metabolic responses in these subjects[11]. These studies provide strong evidence that although TNF cannot generally be detected by the time that life-threatening haemodynamic instability has developed, it is present shortly after bacterial invasion occurs, during the prodromal period. The same studies showed a marked variation between individuals in the magnitude of TNF-release following a standard dose of endotoxin This observation may, in part, explain the well recognized variation between individuals in terms of their symptoms and the pyrexia and cardiovascular responses observed during infections of comparable severity.

The demonstration of TNF in the circulation at the onset of critical illness does not, of course, prove a causal relationship between the molecule and the symptom complex. Recently TNF has been manufactured to a high degree of purity using recombinant technology When recombinant human TNF (rH-TNF) was administered in lethal doses to rodents it produced circulatory collapse and death. Post-mortem findings were indistinguishable from those observed after death from septic shock[12] Dogs receiving sublethal infusions of rH-TNF developed the full spectrum of changes associated with sepsis, including fever, hypermetabolism, hypotension, acidosis and increased pituitary and stress hormone elaboration[13]. When rats received chronic (5-day) infusions of rH-TNF, profound anorexia and fluid retention were also observed[14]. Recently, rH-TNF has been given to humans in clinical trials as a potential antineoplastic agent. The physiological responses that occurred following acute (24-h) infusions were strikingly similar to those occurring following endotoxin administration when the peak plasma TNF levels in the two situations were similar. Responses following rH-TNF infusion occurred more rapidly than following endotoxin, presumably because a latent period was required by the host after endotoxin administration to synthesize and release TNF[15]. When rH-TNF was infused at lower doses over 5 days to humans, fever, marked anorexia and fluid retention consistently occurred[14]

The final evidence that TNF is a principal mediator of

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adverse host changes during sepsis comes from studies in animals where the effects of TNF are neutralized. Mice of the C_3H/HeJ strain have long been known to be resistant to otherwise lethal doses of bacterial endotoxins. It has recently been demonstrated that this strain of mice has a genetic defect that prevents the synthesis and release of TNF[16]. Endotoxin-sensitive mice pretreated with neutralizing anti-TNF antiserum develop marked resistance to lethal doses of endotoxin[17]. Similarly, baboons receiving lethal (LD_{100}) doses of live *E. coli* organisms invariably survived when pretreated with monoclonal neutralizing anti-TNF antibodies[18]. Thus, although a large number of mediators are clearly involved in the cascade that leads to full-blown septic shock, these data suggest that the outcome pivots on the production or otherwise of excessively large amounts of TNF by the host.

These studies have major implications for the development of future strategies to modify the course of severe sepsis in surgical patients. Because TNF is released as a brief pulse following infection, attempts to block its biological effects will generally be likely to be successful if blocking agents are administered very early in the course of the disease, and not when clinical manifestations of septic shock are maximal. Glucocorticoids are potent inhibitors of TNF synthesis and release[16], but this therapy has only proved to be beneficial when these agents were administered to shocked patients almost immediately on arrival in hospital and before any diagnosis was made[19]. Steroid administration later in the course of septic shock has failed to show any benefit[20] and it is possible that the timing of steroid administration in relation to the time at which maximal TNF elaboration occurs following bacteraemia might well explain the discrepancy between results obtained from different groups. It is arguable that similar considerations will apply to the use of monoclonal neutralizing antibodies against TNF.

There is now, however, good evidence that many of the effects of TNF occur through local and systemic activation of the cyclo-oxygenase pathway: many of the reactions that occur following TNF administration *in vivo* are attenuated by inhibitors of the enzyme arachidonate cyclo-oxygenase[11,21]. The initial evidence in both animals and humans suggests that the use of such agents modifies the adverse host responses following injury or infection and diminishes many of the deleterious events associated with TNF elaboration[21–23].

Clinical trials are urgently required to determine if these extraordinarily interesting experimental observations can be translated into improved survival of our critically ill surgical patients.

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Follow-up of two treatment modalities for ductal cancer *in situ* of the breast

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In a mammography screening programme for the early detection of breast cancer 66 cases of ductal cancer in situ *of the breast (DCIS) were diagnosed between 1978 and 1984 and prospectively followed up. In the beginning of the study period, DCIS was treated by mastectomy without axillary clearance but sector resection has been performed increasingly. Since 1982 the latter procedure has become standard treatment. Radical resection was confirmed by specimen X-ray and histopathological examination of whole organ sections. No postoperative radiotherapy was given. Twenty-eight women had mastectomy and 38 had sector resection. The median follow-up times were 77 and 60 months respectively. In the mastectomy group postoperative monitoring did not reveal any local recurrence but one contralateral new invasive cancer was discovered. In the sector resection group five recurrences were found. Three of the latter were new cases of DCIS and two appeared as small invasive cancers (stage I). Mastectomy will cure ductal cancer* in situ *but has a greater morbidity. Sector resection has been established as the method of choice in stage I invasive cancer and is probably also safe in DCIS. The possible beneficial effect of postoperative local radiotherapy after sector resection for DCIS is currently being analysed in a randomized trial which started in Sweden in 1987.*

Keywords: Breast cancer, ductal cancer *in situ*, occult breast cancer, mammographic screening

When mammography was offered on demand to a large fraction of the female population, the number of non-palpable mammary gland malignancies found increased. Since our mammography screening programme started in 1978 this situation has been even more pronounced. Of those malignancies found by mammographic screening, about 10 per cent are ductal cancer *in situ* (DCIS)[1], mostly reported as non-palpable lesions. The question of which is the best treatment for DCIS has not yet been answered. Most data have been collected from the re-evaluation of old biopsy material or reported as the results of treatment by mastectomy[2–4]. Another reason for the controversy concerning the treatment of DCIS is that the histopathological picture is difficult to interpret in some of these lesions. Microinvasive DCIS and some cases of big DCIS of comedo type have probably previously been allocated to the ductal invasive cancer group.

The treatment of all types of breast cancer has by custom been mastectomy, but now stage I cancers and, more recently, stage II cancers are treated with breast-conserving procedures such as sector resection or quadrant resection, mostly with adjuvant radiotherapy. This treatment has also been tried on DCIS lesions. DCIS is only rarely found by clinical examination without the aid of mammographic screening, and therefore individual clinics usually have little experience in the treatment of this type of cancer. Studies of DCIS have therefore to be done on a multicentre basis. Work has already started with the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the European Organization for Research on the Treatment of Cancer (EORTC) programmes in some centres. A similar Swedish multicentre study regarding breast-preserving treatment with or without radiotherapy started in 1987.

The present paper reports the recurrence rate after conservative or ablative surgical treatment of DCIS as seen in a 6-year prospective study.

Patients and methods

Between 1978 and 1984, 66 cases with DCIS were discovered through the current mammographic screening programme in the county of Östergötland, Sweden. The screening procedure is one oblique view mammogram, a short questionnaire about breast disorders answered by the woman, and an inspection of the breast by the X-ray assistant.

All 66 lesions were analysed by mammography and clinical examination, and 44 were further evaluated by fine needle aspiration cytology. When our screening programme started in 1978, mastectomy without axillary exploration was considered to be the treatment of choice for DCIS When breast-conserving procedures became accepted for stage I breast cancer, we also gradually began treating DCIS in the same way, and since 1982 sector resection has been our standard treatment for DCIS[5].

Twenty-eight lesions were treated by mastectomy and 38 by sector resection. No radiotherapy was given Non-palpable lesions in the sector resection group were labelled preoperatively with a needle under mammographic control and a peroperative specimen X-ray was routinely carried out[6].

The excised lesions were histopathologically evaluated after whole organ sectioning[7]. An accurate diagnosis can be made by this technique together with the confirmation of tumour-free margins and the extent of the lesion. Tumour-free margins were stated to be 10 mm, and if the margins were not free or a resection margin was close to a DCIS lesion further surgery was performed. This happened in ten cases Two main types of DCIS are found comedo and cribriform. Patients with microinvasive tumours were excluded from the material The remaining 66 cases represent pure DCIS of the comedo type ($n=32$) or of the cribriform type ($n=34$).

The median follow-up time was 77 months (range 48–106) and 60 months (range 25–100) in the mastectomy and sector resection groups, respectively Five older patients in the mastectomy group died recurrence-free within 2 years of operation and are excluded from the calculation of follow-up time Follow-up was performed as a clinical examination at 6-monthly intervals between 1979 and 1982 and thereafter annually. Mammography was carried out once a year. When recurrences were found, those patients with pure DCIS were treated by

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further sector resection while patients with invasive cancer were offered mastectomy.

Results

The diagnosis of DCIS was reached by a combination of mammography, cytology and clinical evaluation, and verified histologically in 66 patients having a mean age of 61 years (range 40–87).

Mammography

The cases were allocated to five groups depending on degree of malignant appearance. Out of the 66 cases, mammography was declared normal or benign in eight; 24 of the lesions were judged as probably malignant or malignant and 34 had an 'equivocal' mammogram (*Table 1*).

In the majority of cases microcalcification was the dominant pathological finding whereas fibrosis with disturbed architecture was present only in a limited number of cases (*Table 1*).

Cytology

Out of 44 cases in which cytology was performed, 32 were judged to show malignant cells (*Table 2*). Cases with a malignant diagnosis generally represent DCIS of the comedo type. In six cases benign lesions or lesions with slight atypia were observed, whereas the remaining six cases showed atypia.

Clinical findings

In ten cases the lesions were palpable. DCIS was present together with Paget's disease of the nipple in eight cases (*Table 3*). Two patients with palpable tumours and two with Paget lesions had normal mammograms but the presence of a neoplastic lesion was picked up by the questionnaire and the inspection. In four cases the palpable lesions contained mostly fibroadenosis together with the DCIS. A Paget's lesion was present together with a palpable mass in only one case. Blood from the nipple was present in one case with a non-palpable DCIS.

Table 1 *Mammographic patterns and mammography reports in 66 cases of screening-detected ductal cancer* in situ

Mammography report			
Group	*n*	Findings	*n*
Normal	4	Microcalcifications	47
Benign	4	Fibrosis with calcifications	8
Equivocal	34	Fibrosis	7
Probably malignant	20	Normal parenchyma	4
Malignant	4		

Table 2 *Results of fine needle aspiration cytology investigated in 44 cases with ductal cancer* in situ

	n
Benign	3
Slight atypia	3
Atypia	6
Malignant	32
Not performed	22

Table 3 *Clinical presentation and type of treatment given in 66 cases with ductal cancer* in situ

	n	Mastectomy	Sector resection
Non-palpable lesions	56	22	34
Palpable mass	10	6	4
Paget lesions	8	7	1
Blood from nipple	1	1	0

Table 4 *Number of foci in the same breast and type of treatment given in 66 cases with screening-detected ductal cancer* in situ

No. of foci	Mastectomy	Sector resection
1	20	35
2	2	0
≥3	6	3

Table 5 *Distribution of the size (largest diameter) in the 66 cases of ductal cancer* in situ *and between the two treatment groups*

Size (mm)	Mastectomy	Sector resection
0–5	1	7
6–10	9	13
11–20	12	14
21–30	1	3
31–50	5	1

Multifocality. Multifocal DCIS, defined as lesions more than 5 mm apart, was found in 11 cases (*Table 4*). Another four cases also showed lobular cancer *in situ* in parallel with DCIS. Three cases were referred for mastectomy because of the presence of more than three foci of DCIS, but another three with more than three foci still had sector resection as the final treatment.

Size. DCIS foci closer than 5 mm are regarded as one lesion of DCIS, the extent of which is given as the largest diameter (mm). The majority of the lesions had an extent between 11 and 20 mm (*Table 5*). Six cases were between 31 and 50 mm and eight had lesions smaller than 5 mm.

Primary reoperations for radical therapy

Three patients, who were initially offered breast-conserving therapy, were subsequently treated by mastectomy owing to the presence of multicentric DCIS with uncertain margins found at the primary operation. These patients were accurately treated by the mastectomy and are reported in the mastectomy group. Seven lesions in the sector resection group had an uncertainty expressed about the margins and a second resection was done to guarantee clear margins.

Free margins in the sector resection group

After surgery and primary reoperations in the sector resection group, 25 patients had a free margin ≥10 mm, five had a margin of 5–9 mm and another eight had a tumour-free margin of <5 mm.

Follow-up

In total, six cases of recurrent breast malignancy were diagnosed during the follow-up period. These cases were detected by mammography. No case was clinically recognized by palpation

In the mastectomy group, one contralateral ductal invasive cancer (6 mm) was found after 53 months. No local recurrence was observed.

In the sector resection group five relapses (13 per cent) were diagnosed at follow-up. The nature of the primary lesion, the type of relapse and the time interval between the primary and secondary lesion are given in *Table 6*. In three of the cases the primary lesion was DCIS of the comedo type, and in two it was of the cribriform type. Three of the secondary lesions were classified as DCIS, and two were invasive ductal cancers, all but one appearing in the same area as the primary lesion. Three of the recurrences developed in patients with a tumour-free margin of <6 mm.

Monofocal DCIS relapses were treated by a second sector resection whereas multifocal DCIS (case 5) and invasive lesions were treated by mastectomy. In one case of DCIS (case 3) two relapses at different times were found. After the second relapse mastectomy was performed.

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Table 6 *Subtypes of ductal cancer* in situ *at primary operation, histopathology of recurrences and type of second treatment in five cases with local recurrence after sector resection in 38 cases of screening-detected ductal cancer* in situ

Case no.	Primary lesion	Type of recurrence and treatment	Disease-free interval (months)
1	10 mm DCIS cribriform	7 mm ductal invasive cancer + minor DCIS Mastectomy	25
2	15 mm DCIS cribriform	2 mm ductal invasive cancer surrounded with 10 mm DCIS Mastectomy	39
3	14 mm DCIS comedo	9 mm DCIS New sector resection	34
		Second relapse: 2 foci in another part of the breast DCIS-suspect microinvasive Mastectomy	12
4	3 mm DCIS comedo	4 mm DCIS in another quadrant Sector resection	40
5	5 mm DCIS comedo	4 mm DCIS, comedo, in 2 foci Subcutaneous mastectomy	46

DCIS, ductal cancer *in situ* of the breast

Discussion

DCIS is a malignant change in ductal epithelial cells that, by definition, does not penetrate the basal membrane of the mammary ducts. Minor areas of invasive growth may be difficult to detect and the diagnosis must be based on repeated sectioning of the specimen. The whole-organ sectioning technique is especially valuable for the diagnosis of DCIS[7]. DCIS lesions are often multifocal but rarely bilateral. A number of reports indicate a significant fraction of residual multifocal DCIS (about 30–40 per cent) or invasive carcinoma (10–20 per cent), as shown by examination of mastectomy material after breast biopsy or wide excision including the DCIS[3,8–12]. When the DCIS is multifocal, mastectomy is often proposed as being the treatment of choice at least as far as clinical DCIS is concerned. The problem, however, is that we do not know the frequency with which residual DCIS appears as clinically malignant, especially in DCIS discovered by a screening procedure. This is exemplified in a consecutive autopsy case series in which Nielsen *et al.*[13] found 11 cases of DCIS and invasive cancer in 77 women in whom there was no history of previous breast malignancy.

In the present case series, detectable multifocal lesions were found in 11 out of 66 cases (17 per cent). When relapses representing either simultaneous non-detectable malignant cell clones or metachronous lesions are included, five plus one (one case with two recurrences) more lesions are included, giving a total of 17 multifocal lesions in 66 patients (26 per cent) in an approximately 5-year perspective.

With the advent of mammography the ability to detect small malignant lesions has added a new dimension to the subject of disease of the breast In addition to problems regarding the morphological diagnosis of small lesions, including the interpretation of mammographs and fine needle aspiration samples, the variation in biological aggressiveness is probably greater in these occult tumours than in clinically obvious cancers, and is a dilemma for clinical judgement. Until appropriate biological tests are available, all these lesions must be regarded as potentially lethal.

The difficulty in reaching a positive diagnosis is reflected by the fraction of negative findings in both mammography and fine needle aspiration biopsy. Thus, in 58 of 66 cases (88 per cent) and 38 of 44 cases (86 per cent), a malignancy was suspected by the preoperative work-up with mammography and cytology, respectively.

In the present case series 58 per cent of the patients were treated with sector resection and the remainder with mastectomy. In 34 of 56 cases (61 per cent) lesions <20 mm were treated with sector resection (*Table 5*). This procedure was also chosen in two out of three of the cases where only one focus was diagnosed as malignant (*Table 4*) and where the lesions were non-palpable (*Table 3*). Mastectomy was more often employed when two or more malignant foci were observed (eight of 11) and when the tumours were >21 mm (six of ten). The choice of surgical treatment is probably influenced by several factors, including the relationship between the size of the lesion and that of the breast, the surgeon's experience as well as the patient's wishes and, furthermore, by the fact that mastectomy was standard treatment at the beginning of the screening period. Only three patients were converted to treatment by mastectomy. The variation in treatment further reflects the lack of information from prospective randomized case series regarding the various treatments available for DCIS.

Postoperative follow-up including mammography has shown that patients in the mastectomy group were free of disease in 27 of 28 cases (96 per cent) during the follow-up period, whereas the corresponding figure for the sector resection group was 33 of 38 (87 per cent) during their somewhat shorter postoperative observation. Previous studies[14–16] have indicated a relapse rate of up to 67 per cent over a 20-year follow-up period for clinical DCIS

The present case series shows that patients with DCIS run a risk of about 13 per cent of having a recurrence within 5 years if sector resection is chosen as treatment of the primary lesion. This risk must be weighed against the psychological morbidity of losing a breast where the risk of recurrent disease is practially nil. Size of tumour-free margin is probably an essential point to consider. In our material 13 of 38 cases had a margin less than that stated in the written protocol, and three of the recurrences appeared in this group. The present policy of making a wide sector resection around a monofocal DCIS is probably the method of choice in most cases of DCIS, but information from future prospective randomized studies may change this attitude. The benefit of adjuvant radiotherapy is implicated by the NSABP results[17] published in 1986.

Although Bloodgood[18], as early as 1936, wrote a paper where the potentially benign course of intraductal breast cancer was postulated, there is still no scientific evidence to indicate which treatment should be used for the various types of DCIS. Furthermore, it is important to evaluate information from cytometric and steroid receptor analyses to obtain a better basis for selection of patients in which a more aggressive initial treatment should be chosen.

In our opinion, relapses of monofocal DCIS can be treated by a further sector resection. A second relapse of DCIS can perhaps be prevented by irradiation of the remaining breast tissue at the time of the first recurrence. A relapse with invasive cancer in the same area as the primary DCIS lesion may be treated similarly, i.e. a new sector resection plus radiotherapy, even if mastectomy was performed in our two relapses of this type. If the lesion is multifocal or has an invasive component in another quadrant, mastectomy should be offered to the patient. This treatment for local recurrences is currently being investigated in the Swedish multicentre DCIS trial started in 1987.

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High-output external fistulae of the small bowel: management with continuous enteral nutrition

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Three hundred and thirty-five patients with high-output enterocutaneous fistulae arising from the small intestine are reported. Median fistula output was 1350 ml/24 h. Eighty-two per cent of patients were referred from other institutions. The fistula opening was associated with evisceration in 165 cases (49 per cent). One or more severity factors were present in 75·5 per cent of the patients. Patients were divided into three groups according to their initial therapy: 21 patients (6 per cent) referred in a moribund state were not operated on (non-intervention); 80 patients (24 per cent) were operated on as an emergency, and the fistula was either exteriorized or defunctioned; 234 patients (70 per cent) were initially managed conservatively. Appropriate local care and nutrition were provided in all cases. Enteral nutrition was the exclusive nutritional support in 285 patients (85 per cent). In 92 cases with proximal fistulae, methods limiting the fistula output or allowing reinfusion of chyme were required. The overall mortality rate was 34 per cent: 100 per cent in the non-intervention group, 55 per cent after emergency surgery, and 19 per cent after conservative treatment. In the latter group, spontaneous closure was obtained in 88 patients (38 per cent). Overall mortality rate was reduced to 19 per cent in patients treated since 1980. Enteral nutrition with appropriate local care may be used in the majority of high-output enterocutaneous fistulae, with an acceptable rate of spontaneous closure. Conservative management is the treatment of choice in the initial period. Emergency surgery should be restricted to the treatment of haemorrhage or intra-abdominal abscesses associated with uncontrolled systemic sepsis.

Keywords: Small intestinal fistulae, enteral feeding

Modern principles for the management of enterocutaneous fistulae have been formulated over the last 25 years[1–12]. In most reports, the standard technique for the provision of artificial nutrition for these patients is total parenteral nutrition (TPN)[4–8,11–14]. Most authors feel that enteral nutrition with chemically defined diets has only a limited role, and its use is often limited to low-output fistulae[6,15–18].

In the Surgical Digestive Intensive Care Unit of Hôpital Saint Antoine, a referral centre receiving patients from France and other countries, considerable experience in the management of external fistulae has been accumulated. Original techniques to provide enteral nutrition and control fistula output have been developed, allowing the majority of patients to be managed with exclusive enteral support.

The aim of this retrospective study is to describe these techniques and to evaluate the results obtained in patients with high-output external fistulae originating in the small intestine.

Patients and methods

All patients with a postoperative high-output external fistula of the small bowel managed at Hôpital Saint Antoine during the period 1970–86 are presented. 'High-output' is defined as a daily discharge of over 600 ml. There were 335 patients, 198 men and 137 women, of mean age 49·8 years (range 8–85), 82 per cent of patients were referred from other institutions, while 18 per cent were initially operated on at our institution, representing 0·2 per cent of the cases undergoing elective abdominal surgery for the same period.

The primary diagnoses are detailed in *Table 1.* Operations leading to the fistula were performed as an emergency procedure in 40 per cent of cases, and in 17 per cent of patients the indication for operation was a generalized peritonitis. The number of laparotomies before fistula formation ranged from one to six, 72 per cent of the patients having undergone at least two laparotomies. The fistula originated in the jejunum in 117 cases (35 per cent), and the ileum in 218 (65 per cent). The number of openings on the small bowel could be determined in 331 patients. There was a single fistula in 215 patients (65 per cent), two in 69 (21 per cent), and three or more in 47 (14 per cent). A combined urinary fistula was present in 18 cases (5 per cent). The fistula

Table 1 *Primary diagnosis in 335 patients with postoperative external fistulae of the small intestine*

Diagnosis	No. of cases
Lower gastrointestinal tract fistula	220
Colorectal tumour	(45)
Small bowel obstruction	(43)
Appendicitis	(27)
Sigmoid diverticular disease	(27)
Crohn's disease	(19)
Ulcerative colitis	(14)
Radiation enteritis	(13)
Mesenteric infarction	(10)
Miscellaneous causes	(22)
Upper gastrointestinal tract fistula	47
Bile duct obstruction	(17)
Acute necrotizing pancreatitis	(12)
Miscellaneous causes	(18)
Genitourinary tract fistula	38
Abdominal trauma	13
Incisional hernia	9
Others	8
Total	335

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output ranged from 600 to 6000 ml/24 h, with a median value of 1350 ml/24 h.

When the fistula opening was associated with an abdominal wound dehiscence (165 cases, 49 per cent), it was called an 'exposed fistula'[9]. These were divided into two categories according to their mechanism of formation.

1. *Bowel-to-wall* fistulae (127 cases) were secondary to a leak from the small intestine leading to peritonitis which had drained spontaneously (in the absence of reoperation) through a dehisced incision.
2. *Wall-to-bowel* fistulae were secondary to external trauma inflicted on a superficial loop exposed in an evisceration (38 cases).

Fistulae were called 'direct' when the internal opening was visible from the exterior and situated at the level of or close to the external opening (96 cases, 29 per cent). They were termed 'indirect' when the internal opening was not visible and was separated from the external opening by an intermediary track (239 cases, 71 per cent) The origin of the fistula was a disrupted anastomosis in 161 cases (48 per cent), a necrotic lesion in 42 cases (12 per cent) and a traumatic injury in 111 cases (33 per cent), while no precise cause could be found in 21 cases (6 per cent). The time between the operation preceding the fistula and the development of the fistula itself was evenly distributed between 2 and 15 days in 257 cases; seven fistulae developed earlier and 71 developed later.

Associated conditions

The fistulae were associated with diseased bowel in 84 patients (25 per cent): Crohn's disease in 21 cases, short bowel (residual length less than 150 cm as measured at laparotomy) in 25 cases, and radiation enteropathy in 38 cases.

In an attempt to evaluate the severity of the illness, eight severity factors were considered[9]: multiple fistulae (two or more intestinal openings); intra-abdominal abscess (documented by laparotomy, spontaneous drainage, percutaneous drainage, or post-mortem examination); septicaemia (clinical symptoms and positive blood culture), ileus; adult respiratory distress syndrome (mechanical ventilation required), upper gastrointestinal haemorrhage (more than four units of blood in volume); renal or hepatic failure (serum creatinine >250 μmol/l, serum bilirubin >60 μmol/l, aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) greater than three times the upper limit of normal values), thromboembolic complications The incidence of each factor is shown in *Table 2* and the number of severity factors per patient is represented in *Table 3*. In 82 patients (24 per cent) none of these factors was present, and the fistulae in these patients were called 'isolated fistulae'.

Method of management

After initial assessment, one of the three attitudes to treatment was selected: non-intervention, emergency surgery, or medical therapy.

Table 2 *Incidence of severity factors*

Factor	No. of patients	Percentage
Multiple fistulae	116	35
Intra-abdominal abscesses	150	45
Septicaemia	130	39
Ileus	63	19
Adult respiratory distress syndrome	104	31
Upper gastrointestinal tract haemorrhage	60	18
Renal and/or hepatic failure	120	36
Thromboembolic complications	39	12

Table 3 *Number of severity factors accumulated per patient*

No. of severity factors	No. of patients	Percentage	Mortality rate (%)
0	82	24	4
1	69	21	10
2	51	15	20
3	35	10	51
4	38	11	68
5	35	10	80
6	19	6	76
7+	6	2	
Total	335		

Non-intervention. Before 1978, 21 patients were referred in a moribund state and, despite the urgent need for surgery, were considered to be beyond any possibility of recovery. They received simple supportive therapy and died shortly after admission This approach has not been adopted since 1978 when newer techniques in intensive care became available

Emergency surgery In 80 cases, patients were operated on shortly after admission for the following indications: uncontrolled sepsis, acute haemorrhage or evisceration.

Complete exploration of the peritoneal cavity was carried out in 63 patients and the fistula was exteriorized or defunctioned as a temporary stoma. In 19 of these patients, a special procedure was required to close the midline incision without tension[19] In 13 patients, the abdominal wall was left open.

A limited operation for elective drainage of a septic collection or treatment of acute haemorrhage was carried out in 17 cases and the fistula was not dealt with.

Conservative treatment (234 cases) Together with the usual intensive supportive therapy, the two main pillars of medical treatment were local fistula care and nutritional support

Local fistula care comprised irrigation of the fistula track with aspiration of the fistula contents. Irrigation of the fistula track[2] was routinely undertaken with a fine-bore silicone tube and a solution of 0·45 per cent lactic acid instilled at a mean rate of 2500 ml/24 h. Aspiration of the fistula fluid was achieved with a variety of tubes. The basic system consisted of large-bore silicone tubes provided with an air circulation channel and connected to a vacuum bottle regulated at a negative pressure of 50 mbar. In fistulae without parietal dehiscence and with an intermediary track, the irrigation tube was inserted deeply into the track and the fluid was collected by a tube positioned in the track close to the surface or in a simple karaya-sealed appliance to which strong aspiration was applied In direct fistulae with a small external opening, irrigation was superficial and the fluid was collected in a karaya-sealed appliance. In exposed fistulae, the abdominal wall dehiscence was circumscribed by a karaya dam, the irrigation tube was positioned close to the intestinal opening, and the aspiration tube was securely maintained by a wire frame positioned at its most dependent part.

In 64 patients with lateral fistulae that were proximal and well walled off, an attempt was made to limit the fistula discharge by means of an obturating device such as cellulose sponges with lead loads, karaya paste plugs, or infusion of a 3 per cent karaya solution[9]

In 28 patients with lateral proximal fistulae everted in an evisceration, the enteric content collected from the proximal end was reinfused into the distal end[20].

Continuous enteral nutrition This was undertaken as soon as possible after admission or reoperation, and was the exclusive method of nutritional support in 285 patients (85 per cent). Among these patients, TPN was required for a period exceeding 5 days in 71 cases, the mean duration of TPN before conversion to enteral support being 17 days

TPN was the method of nutritional support used in 50 patients, 46 died early after referral and before any attempt at changing to enteral nutrition was possible, while the remaining four patients had less than 80 cm of small bowel remaining.

The diet routinely used for enteral support included glucose polymers, protein hydrolysates, medium chain triglycerides and essential fatty acids. A viscous additive (Amidon-Visco®, Gallia Laboratories, F 92203 Levallois, France) produced a 200-fold increase in the viscosity of the diet, thus slowing intestinal transit and allow absorption of the nutrients from the first 150 cm of small intestine[21] The osmolality of the diet was between 300 and 350 mosm/l, and its caloric concentration was equal to 2·09 kJ/ml at the onset of infusion, reaching 4·18 kJ/ml at full infusion rates. The volume infused and the caloric concentration were gradually increased, and the caloric load after a mean of 10 days reached a plateau of 250·8–459·8 kJ/kg body weight per day. The amount of calories delivered enterally depended on the severity of the sepsis associated with the fistula, as patients with severe sepsis require a higher intake to achieve weight gain[21]. The amount of the enteral intake was also correlated to the fistula output, a higher intake being delivered in high-output fistulae The aim was to achieve a net intake of 209 kJ/kg per day and a positive nitrogen balance of 4–6 g/day

Elective surgery. 120 patients in the group of 234 receiving conservative treatment underwent elective surgery, together with 27 patients who survived emergency surgery and in whom the fistula had been exteriorized as a stoma. Surgical repair of the fistula was carried out after a minimal period of 60 days from the previous operation

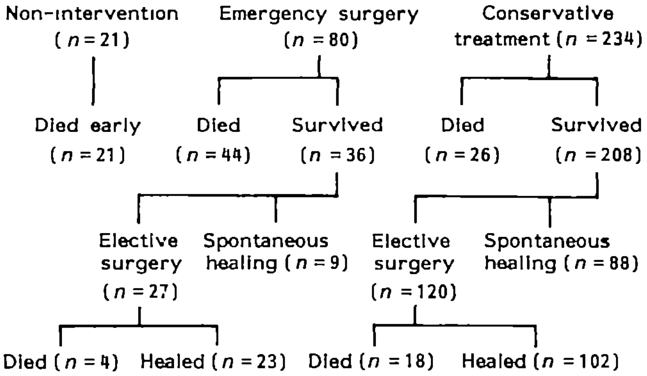
Non-intervention (n = 21)
Emergency surgery (n = 80)
Conservative treatment (n = 234)
Died early (n = 21)
Died (n = 44)
Survived (n = 36)
Died (n = 26)
Survived (n = 208)
Elective surgery (n = 27)
Spontaneous healing (n = 9)
Elective surgery (n = 120)
Spontaneous healing (n = 88)
Died (n = 4)
Healed (n = 23)
Died (n = 18)
Healed (n = 102)

Figure 1 *Outcome of the patients*

Basically the segment of bowel bearing the fistula was excised and the ends were anastomosed but, in the presence of multiple openings into the intestine, lateral suture after excision of scar tissue was preferred.

Results

Therapeutic pathways and mortality

The outcome in the 335 patients is shown in *Figure 1*. The 21 patients in the non-intervention group died shortly after admission. Of the 80 patients undergoing emergency surgery, 44 died early (55 per cent), 27 came to elective surgery (34 per cent) with four deaths, and in nine patients spontaneous closure occurred (11 per cent). In the group of 234 patients managed conservatively, 26 died during the course of supportive therapy (11 per cent). In 120 patients the fistula failed to close and they came to elective surgery (51 per cent); 18 of these patients died. Spontaneous fistula closure occurred in 88 of the patients treated conservatively (38 per cent).

The overall mortality rate was 34 per cent (113 of 335). Survivors remained in hospital for a mean period of 72 days, and a mean of 43 days were spent in the intensive care unit.

Factors influencing survival

Age. The mortality rate was 20–25 per cent in patients below the age of 50 years, rose to 35 per cent in the fifth decade, and reached 45 per cent in older patients.

Time. The mortality rate was 43 per cent before 1980 (209 patients), and 19 per cent after this date (126 patients)

Characteristics of the fistula. Exposed fistulae were associated with a mortality rate of 44 per cent as opposed to 23 per cent in those that were not associated with evisceration ($P < 0{\cdot}001$). Fistula output over 1500 ml significantly increased the mortality rate (39 *versus* 28 per cent, $P < 0{\cdot}05$). Jejunal fistulae carried a higher, but not significantly higher, mortality rate than ileal fistulae (39 *versus* 31 per cent, $P < 0{\cdot}1$). Late development of the fistula (>15 days after surgery) was associated with a slightly better prognosis (25 per cent mortality rate *versus* 36 per cent in earlier cases, $P < 0{\cdot}1$).

Severity factors. Each severity factor significantly affected the prognosis (all $P < 0{\cdot}01$, *Table 4*). The cumulative number of severity factors per patient was closely correlated with mortality rate (*Table 3*). In the absence of severity factors, the mortality rate was only 4 per cent.

Factors influencing spontaneous healing

Among the 234 patients initially managed with conservative treatment, there were 106 exposed fistulae of which 24 closed spontaneously (23 per cent), and 128 fistulae without parietal dehiscence of which 64 healed spontaneously (50 per cent). In the group of wall-to-bowel exposed fistulae, only four of a total of 30 fistulae treated conservatively healed spontaneously (13 per cent).

Patients in whom non-surgical closure of the fistula was achieved were referred at a median time of 9 days after onset of the fistula; the fistula healed after a mean period of medical treatment of 27 days and the total length of time the fistula was present was 39 days (median value). Patients requiring elective surgery were referred at a median time of 26 days after fistula onset, surgical repair was undertaken at a mean of 51 days after admission, and the total length of time the fistula was present was 83 days (median value).

Discussion

TPN has gained wide acceptance in the management of enterocutaneous fistulae. It has also been suggested that bowel rest might favour spontaneous healing[13]. This hypothesis was challenged when reports showed that enteral feeding with elemental diets was also associated with an absence of stimulation of gastrointestinal secretions[18,22], and with a decrease of fistula output similar to that obtained by TPN[16]. Reber *et al.*[6], reporting the results of fistula management with both TPN and elemental diets, showed that equivalent results were obtained in terms of mortality rate and spontaneous closure. Bowel rest and TPN are undoubtedly helpful in terms of nutritional support, fluid and electrolyte control and local care, but it is now widely agreed that healing of the fistula is primarily related to the local anatomical conditions[12,23].

Continuous enteral nutrition has been used since 1965 by our group as a method of nutritional support in the management of enterocutaneous fistulae[21]. It was initially feared that a marked increase in fistula output might occur, but this proved to be the case only in patients with high jejunal fistulae, and that problem has been solved by fistula obturation or reinfusion of chyme The results in the present series attest the validity of this method of nutritional support, as almost all patients could be managed by exclusive enteral alimentation after only a short period of TPN. However, there may be another objection to this mode of nutrition in that polymeric formulae stimulate gastrointestinal secretions and increase both the volume and the enzyme concentration of the fistula fluid. This may result in difficulty in local care and prevent spontaneous healing In fact, these potential drawbacks may be offset by the irrigation of the fistula track, which neutralizes the deleterious effect of the enzyme-rich fistula fluid, and by obturating systems, which obstruct the fistula discharge and provide a favourable environment for tissue granulation and healing.

In the present series, spontaneous healing of the fistula was obtained in 88 of the 234 patients (38 per cent) initially managed with conservative treatment, and spontaneous closure was still seen in 23 per cent of patients with exposed fistulae despite abdominal wall dehiscence These figures are comparable with the results obtained with TPN in recent series, where the rate of fistula healing ranges from 19 to 49 per cent[6,7,12,23–25]. Higher rates of spontaneous healing have been reported from other institutions[4,13,26,27], but comparison between series should be made with care, as the characteristics of the fistulae may differ markedly from one institution to another. Some

Table 4 *Relationship between severity factors and prognosis*

Severity factor	Mortality rate when factor present (%)	Mortality rate when factor absent (%)
Multiple fistulae	48	26
Intra-abdominal abscesses	51	20
Septicaemia	55	20
Ileus	62	27
Adult respiratory distress syndrome	69	18
Upper gastrointestinal tract haemorrhage	62	28
Renal and/or hepatic failure	66	16
Thromboembolic complications	64	30

referral centres deal with a major proportion of complicated cases referred after failure of previous therapy in the initial institution and therefore report a high rate of surgical closure.

With continuous enteral nutrition the prolonged use of intracaval catheters can be avoided. While TPN-related septic complications have reached a low incidence in specialized nutritional units dealing with patients in an acceptable general condition[12,28], they remain a major threat in patients with organ system failure and septic abdominal complications managed in an intensive care unit[24].

Non-intervention in patients thought to be too severely ill to sustain emergency surgery is an approach that we have not adopted in our institution since 1978. Emergency surgery carries a high risk of mortality, and the indications have therefore changed throughout the study period. In the early 1970s, a larger proportion of patients were reoperated on shortly after admission if there was suspicion of intra-abdominal sepsis as we felt that surgical exploration was necessary in such patients referred after multiple operations, in order to evaluate precisely the intraperitoneal lesions. We have now restricted the indications for urgent surgery to major haemorrhage or uncontrolled septic complications.

Conservative therapy is now the treatment of choice in the initial period, the cases considered for late elective surgery being those in which the fistula is not healed after 6 weeks of appropriate management and those where local conditions preclude spontaneous closure (i.e. exposed fistulae with the intestinal mucosa lying in continuity with the surface of the granulation tissue, terminal fistulae and those cases with distal obstruction).

Elective surgery should be undertaken at least 6 weeks after resolution of the signs of intra-abdominal sepsis, this often corresponding to 60–75 days after the initial surgery[10,12,23,29,30]. In the group of patients with exposed fistulae, those due to trauma after evisceration (wall-to-bowel fistulae) may be operated on early after their formation if they occur a long time after the initial surgery.

It should be pointed out that, in our series, patients referred a long time after the onset of their fistula had a lower rate of spontaneous closure than those who were admitted earlier. The reasons for this are probably twofold: firstly, a prolonged period of inappropriate therapy may allow the development of a fibrous and well organized track; secondly, there is a bias in the above comparison as the cases referred relatively late are those where conservative management has already proved unsuccessful.

In conclusion, the mortality rate for high-output enterocutaneous fistulae remains high at around 20 per cent[23,28] despite progress in intensive care and nutritional support. This lack of improvement has already been pointed out[6,7] and is probably related to the increased severity of illness in the patients referred to specialized centres. While simple cases may be managed successfully in the original institution, complex enterocutaneous fistulae should be referred promptly to specialized units[31] where optimal conditions for local management and artificial nutrition are combined. Continuous enteral nutrition associated with special techniques of local care has proved a viable method of support in patients with high-output small bowel external fistulae.

Acknowledgements

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Minimally invasive surgery for the retrieval of complex fractured double J stents

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The increasing use of ureteral endoprostheses over the last 10 years has resulted in the documentation of a number of complications, namely occlusion, migration, perforation, fistulae, stone encrustation and spontaneous fracture. This last situation can result in serious consequences, as disintegration of a stent results in the deposition of multiple friable stent fragments in an already compromised upper urinary tract. We report a patient who had a double J stent inserted to traverse a malignant stricture of the lower third of the ureter and who was referred to our unit with stent fracture.

Case report

A 67-year-old man was diagnosed 6 years previously as having a T_3 adenocarcinoma of the prostate. His right kidney had been removed in the past for stone-related disease. Despite appropriate therapy he presented 2 years later in renal failure with a malignant obstruction of the left vesicoureteric junction. A double J stent was inserted. At the time of referral to our unit he was suffering from recurrent severe urinary tract infections associated with multiple stent fragments in the lower part of the left ureter. Transurethral cystoscopy was difficult because of malignant infiltration of the prostatic urethra resulting in a rigid prostatic fossa. Suprapubic cystoscopy was therefore necessary via a percutaneous track[1]. A direct transabdominal puncture of the left ureter on to the radio-opaque fragments was performed (*Figure 1*). Methylene blue was injected through the needle directly into the ureter, allowing the left ureteric orifice to be visualized. Suprapubic endoscopic urethrotomy of the intramural ureter was then possible allowing instrumentation via the percutaneous cystotomy. The left renal pelvis was opacified allowing a percutaneous nephrostomy tract to be established. Stent fragments were then removed under direct vision using percutaneous antegrade ureteroscopy via the nephrostomy tube with a Fogarty balloon catheter (*Figure 2*).

A good clearance of the left renal tract was accomplished with a few residual fragments remaining in the urothelium. The patient developed no complications after this treatment and has had no further urinary tract infections.

Discussion

The use of straight stents inserted endoscopically into the ureter was first described by Zimskind *et al.* in 1967[2]. A major advance in stents was heralded with the development of the double J stent, the pigtails at either end securing the stent in the kidney and bladder and preventing its migration[3]. No therapeutic advances, however, are without complications.

Although designed for use as temporary prostheses a number of double J stents have been left *in situ* for long periods. It has become apparent that after a sojourn in excess of 6 months[2], these stents are increasingly prone to fracture, although silicone or polyurethane stents are less prone to breakage than polyethylene ones[3]. Fracture of double J stents results in a multitude of fragile fragments within the upper urinary tract, which then result in obstruction and renal colic and may be the focus for persistent urinary tract infections, as shown here.

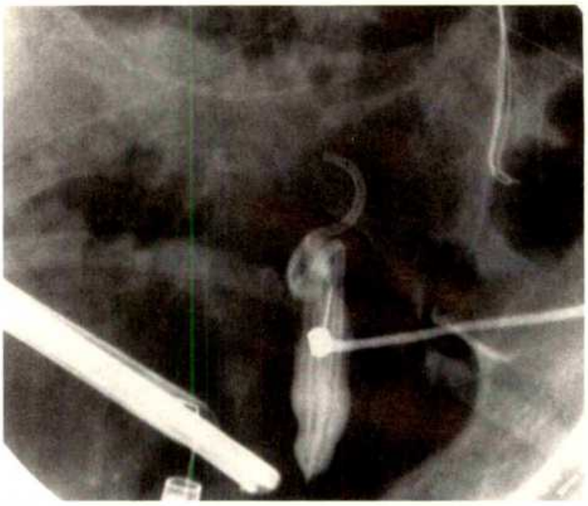

Figure 1 *Direct needle puncture of ureter with opacification. Suprapubic and vesical endoscopies* in situ

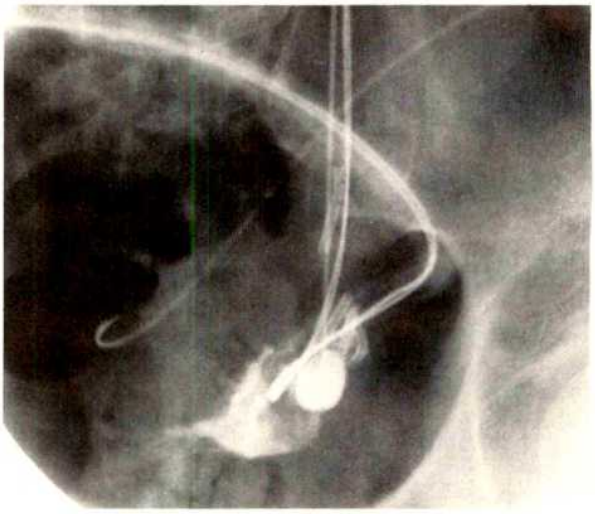

Figure 2 *Retrieval of stent particles with Fogarty catheter*

The retrieval of such a situation presents the endoscopic surgeon with a difficult technical challenge requiring a variety of endoscopic and radiological techniques and expertise. The case reported here demonstrates this and emphasizes the usefulness of the Fogarty balloon catheter technique as the fragility of the stent material precludes the use of biopsy forceps or mechanical snares.

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Colon interposition in children

Since 1960 we have performed 80 colonic interpositions on 79 children. We present a retrospective review of their progress. Sixty-nine interpositions were for long-gap oesophageal atresia, while the remainder followed oesophagectomies, eight for strictures and two others. Overall, the transthoracic route was used in 69 per cent of cases, while 29 per cent were retrosternally placed and one was retropleural. The mean follow-up was 11·08 years. The mortality rate was 12 per cent, with one-third of deaths unrelated to the operation. Graft failure, which occurred on eight occasions (10 per cent), was due to ischaemia in four, intractable stricture in two and stomal ulceration in two. Leakage from the proximal anastomosis occurred in 31 per cent of cases and stricture formation in 27 per cent. Thirty per cent of patients complained of acid reflux, of whom one-third developed stomal ulceration. We present data concerning other complications, including long-term recurrent respiratory infections, malabsorption, gastrointestinal haemorrhage, diarrhoea, intestinal obstruction and redundancy of the graft. Staging the procedure did not affect the outcome, however the higher incidence of serious complications encountered following retrosternal interposition finally led us to abandon this procedure in favour of the transthoracic route. There has been little improvement in the growth rate, but in terms of swallowing ability the outcome was satisfactory in 94 per cent of cases.

Keywords: Oesophageal atresia, oesophageal stricture, oesophageal replacement, colon interposition

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The origins of oesophageal replacement surgery lie with Bircher[1], who in 1907 described a technique for bypassing the oesophagus with an antethoracic skin tube. In 1907 Roux[2] performed the first antethoracic jejunal interposition, and in 1911 Kelling[3] performed the first antethoracic colonic interposition. It was not until 1948, however, that the first intrathoracic colon interposition was described[4]. Since then two techniques have been popularized, that described by Javid[5] in 1954 using a retrosternal route, and that described by Waterston[6] in the same year using a route through the diaphragm, the left chest and the apex of the left pleura. A modification of the latter technique, placing the colon extrapleurally in the normal oesophageal site, after passing through the oesophageal hiatus, was put forward by Freeman and Cass in 1982[7] and reviewed in 1986[8].

From 1960 to 1987, 80 colonic interpositions have been performed on 79 children at the Birmingham Children's Hospital, together with three jejunal interpositions. We present our results and analyse the outcome after prolonged follow-up.

Patients and methods

The indications for colonic replacement of the oesophagus in children are summarized in *Table 1*, but in the vast majority (69) of the 79 cases, long-gap oesophageal atresia was the cause. Exploratory thoracotomy was performed in all cases presenting with a tracheo-oesophageal fistula in addition to oesophageal atresia and in eight cases primary anastomosis was attempted but failed. In children with pure oesophageal atresia, however, exploration was rarely attempted as primary anastomosis is unlikely to be possible owing to a short distal pouch in this group of patients.

Eight interpositions were performed for severe oesophageal strictures which could not be adequately dilated, one followed resection of a benign oesophageal tumour and one was in a patient who had had a successful primary anastomosis for oesophageal atresia but who had an atonic oesophagus and severe reflux, without stricture.

During the same 27-year study period, 432 cases of oesophageal atresia were referred to the Department of Cardiothoracic Surgery at the Birmingham Children's Hospital, giving an overall 'interposition rate' of 16 per cent. This is in keeping with results from other centres: Southampton 25 per cent[8], Iowa 9 per cent[9]. All but three colon interpositions were performed by one of two surgeons (K. D. R. and L. D. A.).

The mean ages of patients at operation for each of the three groups are summarized in *Table 2*.

Of the 79 patients undergoing colonic interpositions, records and follow-up were insufficient in only three. Of the remaining 76 patients, the average follow-up was 11 years and 1 month with a range of 21 days (patient died) to 27 years. In almost all children one or more barium swallows were performed during the follow-up period using both a liquid contrast medium and a solid one (barium soaked marshmallows).

Out of 67 children with oesophageal atresia 25 (37 per cent) had a total of 53 other congenital abnormalities.

Table 1 *Indications for colonic replacement of the oesophagus in children*

	No. of cases
Oesophageal atresia ($n=69$)	
Large gap (36 Type A, 25 Type D)	61
Failed primary anastomosis (8 Type A)	8
Oesophageal stricture ($n=8$)	
Failed anti reflux procedure with repeated dilatations	
Reflux stricture	1
Caustic stricture or congenital stenosis	0
Intractable stricture	
Reflux stricture	7
Caustic stricture or congenital stenosis	0
Other ($n=2$)	
Oesophageal leiomyoma	1
Atonic oesophagus with reflux	1

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Table 2 *Age at operation*

	Mean age (years)	Range (years)
Atresia group	0·9	0·5–2·0
Stricture group	7·0	0·4–15·8
Others	12·3	12·1–12·5

All patients in the atresia group underwent oesophagostomy and gastrostomy before the colon interposition. In 12 per cent of cases the distal oesophagus was absent. Bowel preparation was carried out in all cases and consisted of a low residue feed combined with rectal washouts on the day before surgery. One interposition was performed through a median sternotomy incision, while the remainder were performed through left thoracoabdominal and left cervical incisions (69 per cent), or transverse abdominal and left cervical incisions (29 per cent). Interposition in the atresia group was performed as a single stage procedure in 28 per cent of cases, and as a two stage procedure (initially creating a cervical colostomy with delayed proximal anastomosis) in 72 per cent of cases In the stricture and miscellaneous groups, in all but one case an oesophagectomy was performed at the same time as colonic replacement (itself performed in one stage) All these operations were carried out via a left thoracoabdominal approach.

Overall, transverse colon was used in 79 per cent of cases and ascending colon in the remainder The blood supply was based on the left colic artery in 88 per cent of patients, the middle colic in 11 per cent and on the right colic in one patient All nine interpositions in the stricture and miscellaneous groups involved transthoracic replacement of the oesophagus In the atresia group, however, two grafts became ischaemic even before anastomosis but, of the remaining 66 grafts carried out in 65 patients, 43 (65 per cent) were of the transthoracic (Waterston) type, 22 (33 per cent) were retrosternal and one was retropleural (as described by Freeman and Cass[7]) All grafts were anastomosed to the cervical oesophagus, except for seven of the nine patients in the stricture and miscellaneous groups in whom anastomosis was to the thoracic oesophagus. All grafts were isoperistaltic. Distal anastomosis was to the stomach where the retrosternal route was used, but with the Waterston technique anastomosis was to the distal oesophagus, with the colon's vascular pedicle passed up through a separate (new) hiatus in the left diaphragm. Only where the oesophagus was excised or where a distal segment was absent was the colon and its pedicle passed up through the true 'oesophageal' hiatus.

In two patients, both of whom had had oesophagectomies, a pyloroplasty was performed at the time of colonic interposition In only one other case was a pyloroplasty performed subsequently, but this was in a patient with a retrosternal graft and stomal ulceration who had had an antireflux fundoplication.

A nasogastric or Replogle tube was left in position after proximal colo-oesophageal anastomosis in 47 per cent of cases and an intercostal chest drain was used following a thoracoabdominal approach; it was, however, removed within the first three postoperative days in 82 per cent of patients.

Results

Mortality

Of the 76 patients for whom records and follow-up are adequate, there were nine deaths (12 per cent), seven from the atresia group (10 per cent), one from the stricture group and one following oesohagectomy for a leiomyoma. One death in the early postoperative period was due to multisystem failure following septicaemia from severe respiratory infection after a two-stage transthoracic interposition.

Five deaths were late but related to surgery; one was due to a pulmonary embolus 6 years after the original (two stage retropleural) interposition, but 2 weeks after revision of the distal anastomosis for redundancy. Of the remaining four deaths, one was due to septicaemia and three to respiratory failure after aspiration. Three of these followed a transthoracic interposition and one a retrosternal interposition, two performed in one stage and two in two stages. There were three late unrelated deaths: one due to a cerebrovascular accident, one to influenza and one to an asthmatic attack. These last two patients had had previous failed grafts.

Graft failure

Failure of the colonic interpositions occurred eight times (10 per cent) in seven patients (9 per cent), all of whom were from the atresia group. In two patients the prepared colon graft was found to be ischaemic before anastomosis; in one of these patients a gastric interposition was used instead and in the other a jejunal interposition: both patients have had a successful outcome

Of the five remaining patients, three initially had retrosternal grafts. One was replaced by a transthoracic jejunal graft after failure of the colonic interposition at 4 years due to perforation and bleeding of a stomal ulcer. The second had a gastric interposition for graft failure at 4 years after the development of an intractable stricture. The third patient developed a chronic stomal ulcer which repeatedly bled necessitating graft resection at 9 years. A jejunal graft became ischaemic while the patient was still in the operating theatre and therefore a stomach tube was created from the lesser curve. This too became necrotic after 1 week and was replaced with a jejunal graft supplied in part (distally) by its own vascular pedicle, but with a microvascular anastomosis proximally to the innominate artery and left internal mammary vein.

Two other patients had failed grafts, both after transthoracic interpositions: one was due to an intractable stricture, replaced after 3 years by a gastric interposition, and one was due to necrosis of the graft at 10 days due to ischaemia. In this patient a second graft was fashioned, this time from the right colon, and placed retrosternally, but this also became necrotic at 1 week.

These results are summarized in *Figure 1*. There was no difference in the graft failure rate whether interposition was performed in one or two stages.

Anastomotic complications

Of the 75 viable colonic interpositions, proximal leakage was the commonest anastomotic complication, occurring on 23 occasions (31 per cent), 14 after transthoracic interpositions (27 per cent) and nine after retrosternal interposition (41 per cent). Although leakage occurred more often after retrosternal interposition, this difference was not significant ($\chi_1^2 = 1{\cdot}41$, $P > 0{\cdot}1$). Sixteen were treated conservatively, but seven required revision of the anastomosis. Leakage from the distal anastomosis occurred in only one case. This followed a transthoracic interposition and resolved with conservative treatment.

Stricture formation occurred at the proximal anastomosis on 17 occasions (23 per cent) with a significant difference between transthoracic (eight patients, 15 per cent) and retrosternal (nine patients, 41 per cent) interpositions, ($\chi_1^2 = 5{\cdot}71$, $P > 0{\cdot}02$). One patient developed a distal stricture after a transthoracic interposition and two patients who had had retrosternal grafts developed both upper and lower strictures, as did one patient after a transthoracic interposition.

In only five patients did stricture formation follow an anastomotic leak, but in one such patient, investigated for recurrent respiratory infections 2 months after surgery, a fistula was found between the colo-oesophageal anastomosis and the trachea. This and the stricture were resected, but the stricture recurred and required further resection followed by repeated retrograde dilatations.

In two cases stricture formation eventually resulted in graft failure, but in the remainder operative intervention produced a satisfactory outcome: five required dilatation (antegrade or retrograde) only, and ten required revision of the anastomosis. However, six of these required a further revision of which two required a third revision.

From *Table 3* it can be seen that staging the procedure did not significantly alter the incidence of anastomotic leakage or stricture formation, ($\chi_1^2 = 2{\cdot}44$, $P > 0{\cdot}1$).

In only one patient was there an anastomotic complication related to the colocolostomy. This was a minor leakage which was treated conservatively.

Table 3 *Analysis of anastomotic complications*

Stage	No of interpositions	No. with anastomotic leakage stricture, or both	Anastomotic leakage		Anastomotic stricture		
			Proximal	Distal	Proximal	Distal	Both
1	26 (35)	10 (38)	5 (19)	1	3 (12)	1	2
2	49 (65)	26 (53)	18 (37)	0	11 (22)	0	1
Total	75	36	23	1	14	1	3

Values in parentheses are percentages

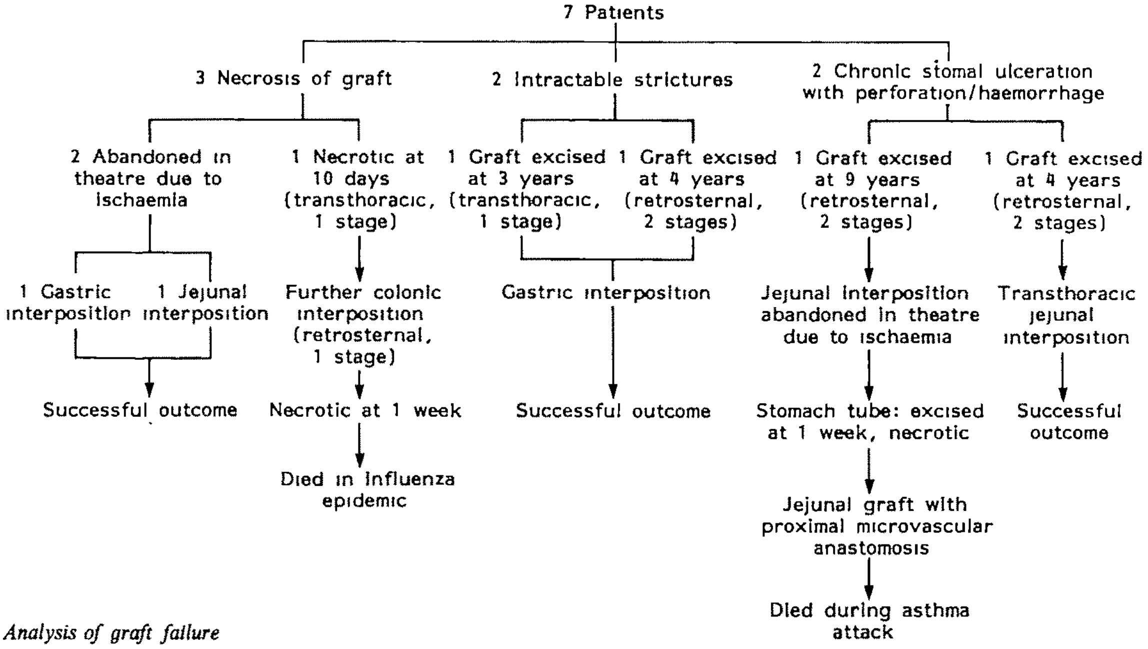
7 Patients
3 Necrosis of graft
2 Intractable strictures
2 Chronic stomal ulceration with perforation/haemorrhage
2 Abandoned in theatre due to ischaemia
1 Necrotic at 10 days (transthoracic, 1 stage)
1 Graft excised at 3 years (transthoracic, 1 stage)
1 Graft excised at 4 years (retrosternal, 2 stages)
1 Graft excised at 9 years (retrosternal, 2 stages)
1 Graft excised at 4 years (retrosternal, 2 stages)
1 Gastric interposition
1 Jejunal interposition
Further colonic interposition (retrosternal, 1 stage)
Gastric interposition
Jejunal interposition abandoned in theatre due to ischaemia
Transthoracic jejunal interposition
Successful outcome
Necrotic at 1 week
Successful outcome
Stomach tube: excised at 1 week, necrotic
Successful outcome
Died in influenza epidemic
Jejunal graft with proximal microvascular anastomosis
Died during asthma attack

Figure 1 *Analysis of graft failure*

All anastomotic strictures occurred in the atresia group, as did all but two cases of leakage, both proximal.

Long-term complications

The most important long-term complication encountered, which finally led to the abandoning of the retrosternal method of interposition in our unit, was the occurrence of acid reflux into the colon graft, leading to ulceration and in many cases to haemorrhage

Six of the 76 patients studied either died too soon after surgery or were lost to follow-up too soon to be included in an analysis of long-term complications. However, in the remaining 70 (50 transthoracic, 20 retrosternal) a total of 21 (30 per cent) patients complained of acid reflux (nine transthoracic, 12 retrosternal), i e 18 per cent of patients with transthoracic interposition developed reflux compared with 60 per cent patients with a retrosternal graft. All but three patients were from the atresia group. Five patients (all retrosternal) required operative intervention as detailed below, but the remainder have been successfully treated with conservative measures

Frank ulceration of the colon graft occurred in seven cases, all with retrosternal interpositions; two of these went on to perforate and bleed, leading to graft failure. One patient who developed an ulcer was treated adequately with medical therapy and one required ulcer excision and fundoplication Three patients developed ulcer-related haemorrhage, two requiring surgery. One of these patients also had colitis and fat malabsorption and subsequently developed melaena which responded to Salazopyrin® (Pharmacia G.B. Ltd., Milton Keynes, UK) therapy These results are summarized in *Figure 2*

In all, gastrointestinal bleeding occurred in nine patients (13 per cent), three transthoracic and six retrosternal. In five patients the haemorrhage was ulcer-related as described above: in two (one retrosternal, one transthoracic) the cause was unknown, in one it was due to mild inflammation of the colon graft, and in one it was due to gastritis, these last two patients and one whose cause was unknown were from the stricture and miscellaneous groups and the remainder were from the atresia group Only four, all ulcer-related, required surgery

The commonest complication encountered was recurrent respiratory infection due to presumed aspiration (although many of these children were asthmatics). This was encountered in 25 children (36 per cent), 17 with transthoracic and eight with retrosternal grafts, i.e. 34 per cent of children with transthoracic grafts complained of recurrent respiratory infections compared with 40 per cent with retrosternal grafts. It is interesting to note that the problem disappeared in one child with a retrosternal graft after having an antireflux procedure performed

Diarrhoea was a feature in 19 children (27 per cent), 12 transthoracic and seven retrosternal, i.e. 24 per cent of those with a transthoracic graft and 35 per cent of those with a retrosternal graft. Two patients also developed malabsorption, one due to colitis

Intestinal obstruction was encountered in 14 cases (20 per cent). Twelve were due to adhesions, six of which required laparotomy Two cases were due to internal hernias, one through the diaphragm and one through the transverse mesocolon.

Anaemia developed in seven patients (10 per cent) In one it followed transthoracic interposition and was due to renal failure and in the remainder it followed retrosternal interposition and was due to gastrointestinal bleeding (four) or unknown causes (two). Halitosis was reported in nine children, seven after transthoracic interpositions Redundancy of the colonic graft occurred in four cases (6 per cent, three transthoracic). Three required no specific treatment, but one required side-to-side cologastrostomy (transthoracic graft). Wound dehiscence occurred in three cases (4 per cent) all after transthoracic interposition via a thoracoabdominal incision. A permanent

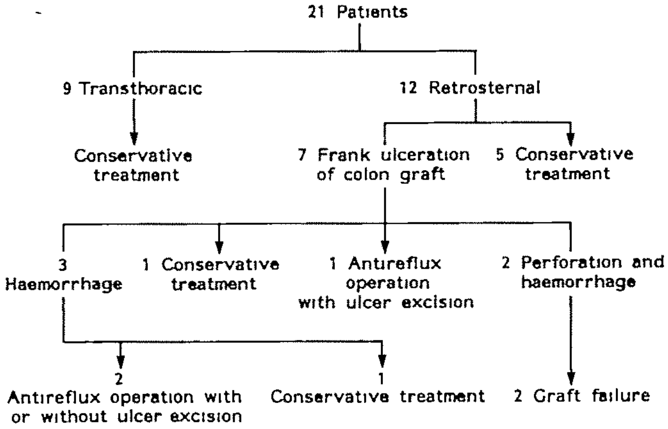

Figure 2 *Analysis of acid reflux*

Table 4 *Analysis of outcome*

	Outcome			Normal diet	
	Excellent	Good	Fair	Yes	No
Atresia group					
Transthoracic	18	16	2	35	1
Retrosternal	2	11	—	12	1
Stricture /other group					
Transthoracic	4	2	1	6	1
Retrosternal	—	—	—	—	—

left recurrent laryngeal nerve palsy occurred in three patients (4 per cent) postoperatively, all after transthoracic interposition and one patient (transthoracic) developed a left phrenic nerve palsy.

Although other complications, such as dumping and Horner's syndrome have been reported[10,11], no such complications were apparent in our series. Despite a 20-year follow-up in some patients, diverticulosis and carcinoma of the colon graft have not been observed so far.

Outcome

Excluding patients who died, required second grafts, had inadequate records, were lost to follow-up or had follow-up of less than 1 year, there remained 56 with a successful colonic interposition in whom we were able to assess the long-term outcome and 51 in whom we were able to follow the pattern of growth and development (mean follow-up 14·0 years, range 2·4–26 years).

The outcome in terms of dysphagia was classified as follows, according to the criteria adopted by Ahmed and Spitz[12]: excellent, asymptomatic, normal diet; good, predominantly asymptomatic, but occasional dysphagia; and fair, significant dysphagia with or without repeated dilatations.

Only three patients (5 per cent) reported anything less than a good or excellent result, however, those who had had a retrosternal graft were less likely to be completely free of dysphagia than those who had had a transthoracic interposition. In the atresia group 50 per cent of transthoracic patients had an excellent result compared with 15 per cent of retrosternal patients. However, virtually all patients were able to eat a normal diet (*Table 4*)

Analysis of growth curves revealed that 75 per cent of patients in the atresia group who required colonic interposition had a birthweight at or below the 25th percentile but that, overall, the trend as growth occurred was to remain below the 25th percentile for weight and height: at follow-up 85 per cent were below the 25th percentile for weight and 67 per cent were below the 25th percentile for height.

Records and follow-up for patients surviving in the stricture group are adequate in only two cases, but it is interesting that both of these patients underwent substantial growth spurts from below the 50th to above the 75th percentile.

Discussion

The commonest indication for oesophageal reconstruction in children is long-gap (greater than 6 cm) oesophageal atresia. If primary anastomosis is impossible, delayed primary anastomosis may be attempted after a period of elongation of both the proximal and distal pouches by a variety of methods of bougienage[13,14], possibly supplemented by a circular myotomy of the upper segment[15]. If this fails to produce adequate length, some form of interposition is required. The simplest form of oesophageal replacement in these children, and for others who have undergone oesohagectomy for strictures, tumours or other reasons, is total gastric transposition with intrathoracic oesophagogastrostomy. This approach was once unpopular owing to the high incidence of reflux, oesophagitis, stricture formation and nutritional and growth problems that occurred in children. However, recent results reported by Spitz[16] are more encouraging.

A reversed gastric tube constructed from the greater curve of the stomach has been used with some success[17–20], but it necessitates a long suture line which is prone to leakage. Reflux of acid leading to oesophagitis is also a problem, and in infants an intrathoracic stomach, whether present as a tube or in its normal state, represents a large volume which, especially when distended with air, can severely compromise lung function.

Jejunal interposition has been used with some success[21] and has the advantage of being a conduit of appropriate size which retains vigorous peristalsis. However, the vascular pedicle is invariably short and restricts the length of jejunum that can be used. In children especially, the blood supply is even more precarious and rarely is it possible to achieve a proximal anastomosis above the level of the aortic arch. In our series three jejunal grafts were fashioned after failure of colonic interposition. In one of these patients the graft was abandoned at operation because of ischaemia, but the other two have had a satisfactory long-term result and neither has developed alkaline oesophagitis.

Improvements in microvascular techniques have led to the use of free jejunal grafts. Initial experience involved drawing up a loop of jejunum into the neck based on a mesenteric vascular pedicle, but augmenting the blood supply by anastomosis of a part of the vascular arcade to the internal mammary vessels in the upper part of the chest. This technique was described by Longmire[22] and a modification was used by us in one patient with atresia aged 17 years who had previously had multiple graft failures; venous anastomosis was to the internal mammary vein and arterial anastomosis via a saphenous vein conduit, to the innominate artery. The outcome from this was successful with a good functioning graft, but unfortunately the patient died 7 months later from unrelated causes.

More recently experience in the use of totally free jejunal grafts has been gained in several centres, notably Emory University (Atlanta, Georgia, USA). Jurkiewicz[23] reports only a 10 per cent graft failure rate in 55 patients which compares favourably with any other method available. However, this procedure requires a degree of technical skill that would limit its use to only a few centres. Furthermore, the patients reported in this series were all adults. However, the application of this technique to children remains much less clear because of the small size of the vessels concerned.

In 1986 Halsband[24] reported a further method of interposition using a free autologus jejunal mucosal conduit. Based on the observation that after Livaditis myotomy[15] there remains only a mucosal/submucosal tube bridging the gap, with secondary coating by fibrous tissue and, after Rehbein's olive and thread method[14], a channel is created from mediastinal granulation tissue with secondary oesophageal mucosal lining, H. Halsband, U. Brockmuller and M. Volpel (unpublished results) have tested whether long-gap oesophageal atresia in animals could be bridged by a free transplanted autologous mucosal/submucosal jejunal tube. Provided the grafts were splinted and bougienage was performed during the period of maximal wound contraction, the results after 6 years follow-up were impressive. This technique has now been tried in two neonates and results are again encouraging

Colonic interposition is currently the most popular form of oesophageal replacement in children with a preference for use of the left colon: this is less bulky than the right colon, more used to propelling a solid than a liquid bolus, and does not involve sacrifice of the terminal ileum, with its consequent impairment of vitamin B_{12} absorption[26]. In addition, the left colon has a more favourable blood supply based on the left colic artery which, when the colon is drawn up into the chest, comes to lie in a straight line, with no kinking. However, in our series there were no anastomotic complications in the five patients with a transthoracic interposition using the right colon and in the 12 patients with retrosternal interpositions using the right colon, the incidence of leakage and stricture formation was 58 per cent and 33 per cent respectively, compared with 20 per cent and 50 per cent in the ten patients where left colon was used.

The most popular route for the interposition is that described by Waterston[6] The main alternative is the retrosternal position, which still has some proponants[27] but which was abandoned by us because of an unacceptably high rate of complications, in particular, anastomotic leakage and stricture formation, acid reflux, long-term recurrent respiratory infection, anaemia and diarrhoea. In addition we have observed a worse overall long-term result in terms of dysphagia.

In contrast to our experience, Lindahl *et al.*[20] showed no statistical difference in results from 34 patients with retrosternal or transthoracic interpositions. Nevertheless they observed that their single case of an anastomotic ulcer occurred in a retrosternally placed colon. In our series 35 per cent of patients with a retrosternal graft developed an anastomotic ulcer compared with none following transthoracic interposition. This difference may be explained by the increased incidence of acid reflux found after retrosternal interposition (60 per cent compared with 18 per cent after transthoracic interposition), it is perhaps not surprising as with the retrosternal approach, anastomosis is directly to the body of the stomach, whereas with the Waterston procedure it is usually to the distal oesohageal stump, thus preserving the integrity of the normal antireflux mechanisms In addition the Waterston technique has the advantage of enabling a shorter length of colon to be used to replace only that proportion of the oesohagus which is absent.

In our series and in others[12,28] there does not appear to be any advantage in staging the procedure unless the vascularity of the colon segment is in doubt[29,30]. What may be more important, however, is the timing of the procedure. It has generally been thought that the mortality rate of corrective surgery is higher in small infants with oesophageal atresia, owing to the greater potential hazard of regurgitation and aspiration. Furthermore, in the absence of a tracheo-oesophageal fistula, children with oesophageal atresia usually have a small colon and stomach with a poorly developed blood supply. For these reasons Waterson favours 6–12 months as the optimal age for replacement surgery. Nevertheless, Freeman[8] has recently proposed early interposition at 2 weeks following just an initial gastrostomy and Replogle tube drainage of the upper pouch So far this policy has had good results. If corrective surgery is delayed, however, sham feeding is certainly important to avoid feeding difficulties once gastrointestinal continuity has been restored.

What may also be important, particularly in view of the high incidence of chest infection and the fact that most early complications arise from vascular insufficiency, is elective postoperative ventilation to ensure adequate oxygenation during the most critical period[31]. Similarly, it is important to correct hypovolaemia and to maintain an adequate blood pressure particularly in the first few hours after surgery.

The topic of motility in the colonic conduit has caused considerable controversy. Early work based on fluoroscopy, cineradiography and manometry concluded that the conduit emptied by gravity alone and that there was no propulsive motor activity[30,32]. In support of this Sieber and Sieber[32] reported that no difference in function could be found between grafts placed in the isoperistaltic or the antiperistaltic positions However, recent work[33–36] suggests that there may be some degree of propulsive motor activity in isoperistaltic grafts, but more importantly there appears to be better clearance of an acid load. In addition Clark *et al.*[35] found prolonged periods of alkaline recordings during 24-h pH monitoring of the infradiaphragmatic colon and they have postulated that the bicarbonate-containing mucus secreted by the colonic mucosa may further help to protect against acid reflux. For these reasons and from our own experience we would not advocate antiperistaltic grafts.

Redundancy has frequently been reported after colon interposition[8,10] and may be a serious problem. However it is our experience that this is generally not so and usually no specific treatment is required although symptoms do not necessarily improve as the child grows because the colon also grows. What appears to be a more serious problem, and it may have been underestimated in the past, is haemorrhage. This occurred in 13 per cent (nine) of patients and led to graft failure in two cases.

Aspiration-induced respiratory infection occurring in the postoperative period has been well documented[12] However, to the best of our knowledge, there are no reports concerning the incidence of recurrent respiratory infections occurring on a long-term basis. In our experience 36 per cent of children complained of this problem several years after interposition. While many are also asthmatics, undoubtedly aspiration is frequently responsible. Perlmutter *et al.*[37] reported a single case of colobronchial fistula occurring 14 years after colonic interposition. Although extremely rare, this possibility should be considered where recurrent respiratory infection is a new feature and has not been present since operation.

In keeping with most other series[12], we did not demonstrate any 'catch-up' phase in the growth rate after colonic interposition for oesophageal atresia Interestingly German and Waterston[38] found no difference in weight gain between patients treated by primary anastomosis and those treated by colonic interposition, but they observed that those requiring interpositon had a consistently lower birthweight and they postulate that these patients represent a group of small-for-date babies. Long-term experience of this condition is that one-third remains small over a 5-year period[39].

The pattern of growth after interposition for an intractable stricture appears to be different from that observed in atresia patients[40], but the numbers involved in our series are too small to comment.

In common with Ahmed and Spitz[12] we have observed that many of the initial problems after colonic interposition (respiratory infection, dysphagia and so on) improve with time and we believe it is important to stress this to the family concerned, particularly as psychological disturbances related to the problems of adjustment are known to occur in both the child and the family

Whether the interposed segment of colon, which, when the operation is performed in infancy, is likely to remain *in situ* for 70 years or more, is more likely to develop diverticular disease or carcinoma than a normally sited segment of colon remains to be seen, but both conditions have already been recorded[25,41] although resection and reanastomosis have been possible

In summary, we believe that colonic interposition is a satisfactory method of oesophageal reconstruction in children with relatively low mortality and failure rates. By adopting a policy of transthoracic (Waterston) interposition we have significantly reduced our complication rate from earlier attempts using a retrosternal route, and we believe that many minor problems encountered in the early years after surgery disappear with time

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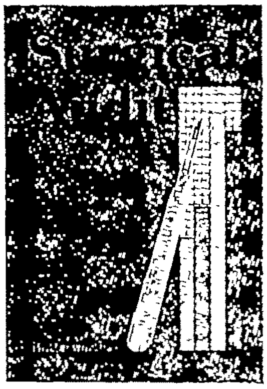

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Umbilical sepsis

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Pilonidal sinus of the umbilicus is rarely reported, and there are only 17 reported cases. On reviewing the records from Jordan University Hospital, 24 patients who were treated surgically for a discharging umbilical sinus were found. Three patients had known causes for their umbilical sepsis, namely stitch sinus, urachal remnant and an umbilical polyp. Of the remaining 21 patients, seven had clinical and pathological evidence of hair in their umbilicus. Most of our patients were young men who presented with discharge, soreness or pain, swelling, and cellulitis. Treatment by umbilical excision, leaving the skin defect to heal by secondary intention, proved satisfactory. The resultant scar resembles a normal umbilicus.

Keywords: Umbilicus, sepsis, pilonidal sinus, omphaloplasty

The first description of a patient with a pilonidal sinus was by Anderson in 1847[1], and Jackson[2] described pilonidal sinus in the umbilicus in 1854. The term pilonidal sinus was first proposed by Hodges[3] in 1880. Pilonidal sinus was originally thought to be congenital in origin, but the works of Patey and Scarff[4] on interdigital pilonidal sinus in barbers, and Patey and Williams[5] on the arrangement of hair in the pilonidal sinus of the umbilicus strongly suggest that this disease is acquired[6].The case reported by Colapinto[7] proves beyond doubt that pilonidal sinus of the umbilicus is acquired as the patient was a barber and the hair found in his umbilical sinus was of different colours and therefore belonging to his customers. There are reports of 17 cases of umbilical pilonidal disease in the literature[2,5,7–20]. A further seven cases of pilonidal sinus from a total of 21 patients who presented with umbilical discharge or suppuration are presented. We propose a simple method of treatment for this disease which can be safely and effectively applied to treat the acute and chronic variety of the disease.

Patients and results

The records of 24 patients with a discharging umbilical sinus treated at Jordan University Hospital between 1979 and May 1988 were reviewed. Three patients had known underlying causes (a stitch sinus following laparoscopy, a urachal remnant, and an umbilical polyp) and were excluded from further study. The remaining 21 patients comprised 19 men and two women. Their ages ranged from 18 to 45 years with a mean age of 21 years. All patients complained of a discharging umbilicus, 13 patients had localized pain, eight had swelling with cellulitis around the umbilicus, six had pyrexia and leucocytosis, and one had enlarged axillary lymph nodes. The duration of symptoms ranged from 3 days to 4 years (mean 6 months). Seven patients (six men and one woman) had clinical evidence of hair in their umbilicus. One patient who was advised to use a dilute alcohol cleansing solution developed severe suppuration requiring emergency surgery. The degree of hirsuitism was not mentioned in the records.

Nineteen patients were treated surgically; two patients did not attend for treatment. Six patients were treated by elliptical excision of the umbilicus with primary closure. Six patients were treated by excision and primary reconstruction of the umbilicus. The remaining seven patients (treated by A.S.S.) underwent excision of the umbilicus with a surrounding disc of tissue down to the rectus sheath, a technique which we describe as omphaloplasty by secondary intention. The resulting wound was cleaned with saline daily, dressed with dry gauze, and left to heal by secondary intention. Complete healing of the wound took approximately 1 month. The resultant scar looks like a normal umbilicus, giving a very satisfactory cosmetic appearance (*Figures 1* and *2*).

The mean duration of hospital stay did not differ between patients treated by the closed method (4·2 days) and those treated by the open method (4·4 days). Two patients treated by the closed method developed wound infection requiring drainage whereas none of those treated by the open method had significant infection.

The histopathology showed evidence of acute inflammation and foreign body granuloma in all patients. In addition the presence of hair was noted in seven patients.

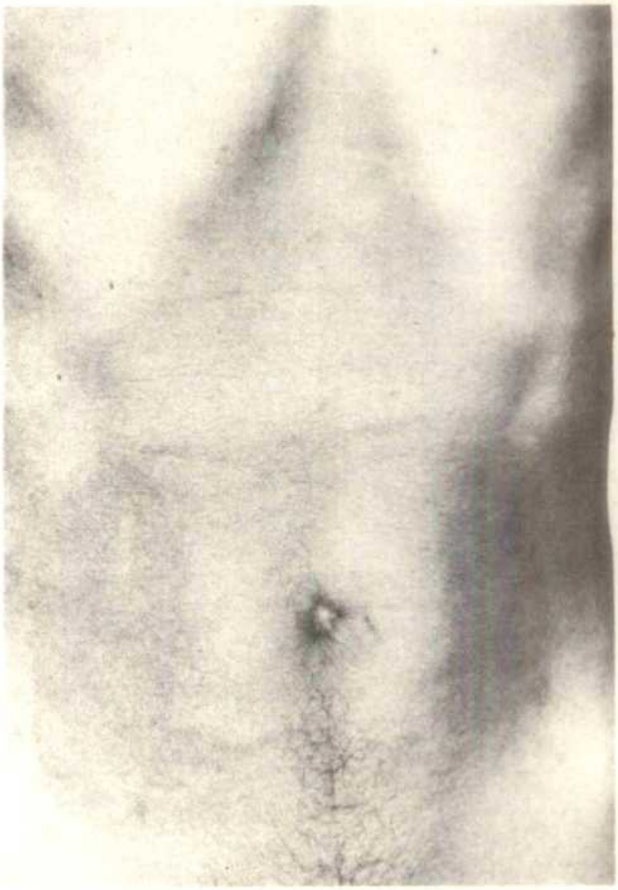

Figure 1 *The scar after complete healing in a male patient*

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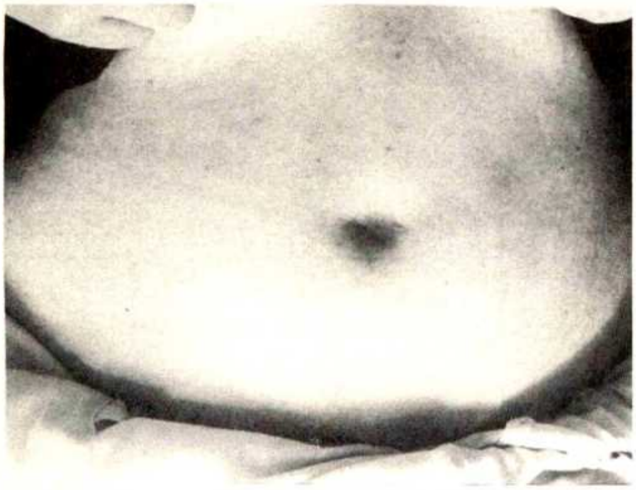

Figure 2 *The scar after complete healing in a female patient*

Discussion

Pilonidal sinus of the umbilicus is a rare disease. Only 17 cases have been reported in the literature[2,5,7–20]. Goodall[12] reported 163 cases of pilonidal disease; only one involved the umbilicus, making an incidence of 0·6 per cent. It is a disease of young hirsute adult men. The only woman to be reported had an umbilical discharge without clinical evidence of hair in the umbilicus; she did not undergo surgery and Aird[8] could not have made a definite diagnosis. The mean age of reported patients was 25 years (range 18–56 years) and did not differ significantly from that in our series. Of our total series of 21 patients, seven had clinical evidence of hair in the umbilical sinus. There were two women and one of them had hair in the depths of the umbilicus. The disease affects people with different complexions as three of the cases reported had dark skin (two Indians[5,16] and one not specified[9]), thus claims that the disease occurs mostly in young hirsute Caucasian men[19] seems unjustified.

The majority of reported cases have been symptomatic[9] and the symptoms were sometimes intermittent with an average duration of 15 months (range 0·5–72 months). All our patients had symptoms and signs which were similar to those reported with an average duration of 6 months (range from 3 days to 4 years). They included pain, soreness, swelling, cellulitis, and discharge. Six patients had pyrexia and leucocytosis. Axillary lymphadenitis was recorded in one patient with marked umbilical suppuration which followed the liberal use of a cleansing solution; she was treated by emergency omphaloplasty by secondary intention as described earlier. There are four reports of coexisting pilonidal sinus of the umbilicus and sacrococcygeal region[16–19], but none of our patients had this combination. Gupta and Gupta reported a case of umbilical pilonidal sinus with urachal adenoma[20] and one of our patients with umbilical discharge had a urachal remnant.

Various treatments for pilonidal sinus of the umbilicus have been described. Hardaway[10] and Sadeghi-Nejad and Rains[9] report treatment by simple extraction of the hairs and claim healing of the sinuses. The condition of the patient reported by Mayo *et al.*[11] became worse by the use of a cleansing solution and antibiotic ointment before undergoing surgery. This was also our experience with one patient using a dilute alcohol cleansing solution. We would therefore stress the importance of keeping the umbilicus dry in addition to removing the hairs in the conservative management of this condition.

In the 17 cases of pilonidal sinus reported in the literature, surgical treatment was most commonly employed, omphalectomy with primary suture being performed on 11 occasions. Excision and primary reconstruction of the umbilicus was performed on three occasions[7,19,20], and in one instance it was preceded by incision and drainage 6 weeks earlier for severe suppuration[7]. Nineteen of our patients were treated surgically. A simple method of treatment for this condition (omphaloplasty by secondary intention) is proposed. It is safe and can be used as a definitive treatment in all patients with different grades of infection, avoiding the need for incision and drainage as an initial step in those with suppuration, and finally on healing it creates a new cosmetically acceptable umbilicus.

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Direct method of measuring venous ulcers

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In venous ulcer studies the end-point is complete re-epithelialization, but it is useful to know the initial ulcer area and healing rate. Several methods have been described for measuring ulcers, the simplest involving measurement of the length of the long and short axes using a ruler[1,2] or tracing the ulcer outline on to a transparent plastic sheet. The digitizing tablets of computers and photographic techniques have been used to estimate areas and circumferences[3–7]. The complex three-dimensional technique of stereophotogrammetry has also been applied to this problem[8].

None of these techniques gives an immediate indication of ulcer size. A device that makes direct measurements, without intermediate steps, may save time and increase accuracy. We have used a sonic digitizer (GP-7 Grafbar model, Scientific Accessories Corporation, Southport, Connecticut, USA) for measuring venous ulcers and compared this with other techniques. The digitizer has a stylus with an ultrasonic pulse generator at its tip (*Figure 1*). The pulse is initiated by a hand-held microswitch and picked up by two point microphones. Internal timing circuits enable the position of the stylus to be estimated to an accuracy of 0·1 mm. The Cartesian co-ordinates of the digitized point were then sent to a BBC microcomputer (Acorn Computers Ltd., Cambridge, UK) to display the traced shape on the screen, and to calculate the area and circumference of the traced object.

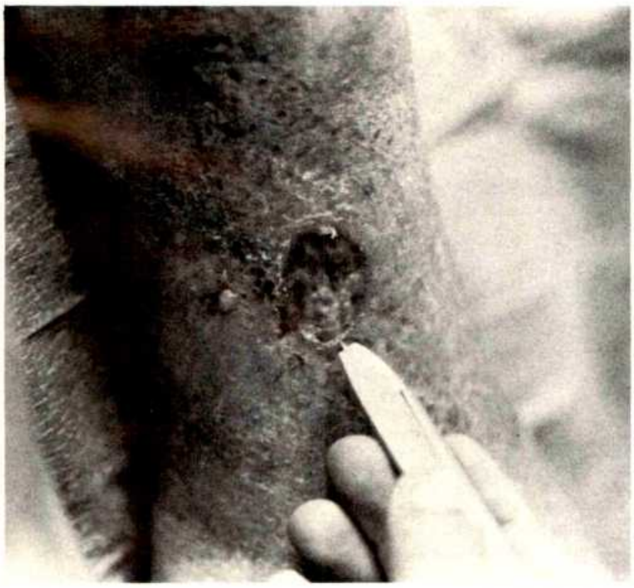

Figure 1 *The sonic digitizer used to measure an ulcer. The stylus is used to point to the edge of the ulcer, while the traced shape appears on the computer screen. The computer also calculates the area and circumference of the ulcer*

The ulcers of 32 patients attending the venous clinic at the Middlesex Hospital were measured by three techniques, each being used three times and average figures calculated for circumference and area:

1. The ulcer was traced on to a transparent plastic sheet of uniform weight. The circumference and area were measured using a digitizing tablet (MOP, Kontron, FRG)
2. The traced areas were then cut out and weighed on a laboratory balance to a resolution of 100 μg, allowing calculation of the area
3. The sonic digitizer was positioned so that the ulcer was in the active digitizing area, ensuring that sound reached the digitizer microphones by travelling over the surface of the leg, correctly indicating the dimensions of the ulcer. The digitizer stylus was used to point to the edge of the ulcer at 5-mm intervals while pressing the push-button switch to initiate ultrasonic pulses. The ulcer outline, area and circumference were displayed on the screen of the microcomputer. Large or circumferential ulcers were measured in two or more sections.

The regression line and Pearson's correlation coefficient for the sets of data were calculated using the least squares technique. The correlation coefficient between the weighing technique and the sonic digitizer was 0·98, and between the MOP area measuring device and the sonic digitizer it was 0·99. The correlation coefficient between the circumference measured indirectly by the MOP and the sonic digitizer was 0·995. In each case the slope of the regression line was very close to 1, lying in the range 0·98–1·02.

There was no difference in the time required to trace the ulcers with the sonic digitizer or using a plastic sheet, about 30–60 s being required for either technique depending on the size and shape of the ulcer. The area or circumference was immediately available from the sonic digitizer, but further time-consuming cutting or tracing was necessary to find the area by either of the other two techniques. These results confirm the accuracy of the sonic digitizer as a rapid and useful method of measuring venous ulcers.

The cost of the digitizer is £1500 sterling including software, which is also available for IBM compatible computers (PMS Instruments Ltd., Maidenhead, UK).

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Intraoperative immunostaining for detection of invasive cells at the resection margin of Borrmann type 4 gastric carcinoma using monoclonal antibody S202

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Borrmann type 4 gastric cancer is clinically characterized by diffuse infiltration with carcinoma cells. An antiscirrhous carcinoma monoclonal antibody (MAb) S202 was used in a rapid immunostaining procedure to identify the limit of tumour invasion during surgery in samples obtained from the resection margins in 37 cases of Borrmann type 4 gastric cancer. In two instances, conventional cytological diagnosis using haematoxylin and eosin staining was negative, and in another it was inconclusive; whereas by the rapid immunostaining method single cells stained darkly, indicating malignancy. In two specimens, a positive diagnosis could be made by both methods, but immunostaining of these sections served to highlight the adenocarcinoma cells against the inflammatory background: further resection was performed. This technique enables clear recognition of the infiltrating tumour cells in the frozen sections of resected specimens. The rapid immunostaining method using MAb S202 allowed accurate and rapid determination of the limit of tumour extension at the surgical margin during surgery.

Keywords: Gastric cancer, Borrmann type 4, rapid immunostaining method, monoclonal antibody S202

Borrmann type 4 carcinoma cells extend through the gastric wall without glandular formation[1–3]. At the time of surgery, it is difficult to discriminate microscopically invasive carcinoma cells from inflammatory cells at the resected surgical margin using a frozen section technique. In addition, as the malignant cells are dispersed and resemble reactive inflammatory cells, staining with haematoxylin and eosin does not always permit identification of malignant cells by standard cytological criteria.

Our attention has been focused on the detection of antigens specific for carcinoma cells, but not inflammatory cells. Such antigens were found in the cytoplasm of gastric cancer cells (*Figure 1*). Monoclonal antibody (MAb) S202 was generated by using an intact scirrhous gastric carcinoma cell line, MK-01, for immunization[4–7]. A previous study indicated that immunoperoxidase staining can be performed within 15 min using biotin-labelled MAb S202[6]. This method has been evaluated to determine the limit of invasion of Borrmann type 4 gastric cancer at the resection margin during surgery.

Patients and methods

In 37 cases of Borrmann type 4 gastric carcinoma, specimens were obtained from the resection margin of the tumour at the time of surgery. Immediately after being cut, the frozen sections were fixed with acetone for 3 min. The staining procedure has been described previously[6]. Briefly, the sections were treated with biotin-labelled S202 (20 μg/ml) for 5 min, and avidin–biotin peroxidase complex for 3 min, with a 10-s phosphate-buffered saline wash between each step. The immunoperoxidase was made visible by incubating the sections with a solution of 0.06 per cent diaminobenzidine and 0·01 per cent H_2O_2 in Tris buffer (pH 7·4) for 3 min. The slides were finally counterstained with haematoxylin for 1 min and mounted.

The histological differentiation of the tumours was graded from the haematoxylin and eosin stained sections. The tumours were graded according to the predominant histological pattern of differentiation. The resection margin with a rim of at least 0·5 cm of normal mucosa surrounding the resected tumour and not containing tumour cells was defined as tumour-negative. When single cells stained with haematoxylin and eosin were judged to be malignant by conventional cytological criteria, the sections were defined as positive. When the diagnosis of cancer was difficult by cytological criteria, the sections were judged as suspicious. When staining with MAb S202, a clearly defined dark-brown precipitate in the cytoplasm of single cells was judged as positive. The results of haematoxylin and eosin staining and immunostaining of the frozen sections were compared later with those obtained on the permanent formalin-fixed slides.

Results

Eight of the 37 specimens had a signet-ring-cell carcinoma and the others were poorly differentiated adenocarcinoma. In two cases, conventional cytological diagnosis using haematoxylin and eosin staining was negative and in another it was suspicious, but the immunoperoxidase findings were positive (*Table 1*). The immunostained cells were clearly distinguished from the inflammatory cells (*Figure 2*). In two specimens, the diagnosis was positive with both methods.

In cases diagnosed as positive, further resection was performed. The results were confirmed later by those obtained on the formalin-fixed slides.

Table 1 *Correlation of cytological and immunohistological diagnosis of carcinoma cells at the resection margin obtained from Borrmann type 4 gastric cancer samples*

	Immunohistological diagnosis	
	Negative	Positive
Cytological diagnosis		
Negative	32	2
Suspicious	0	1
Positive	0	2

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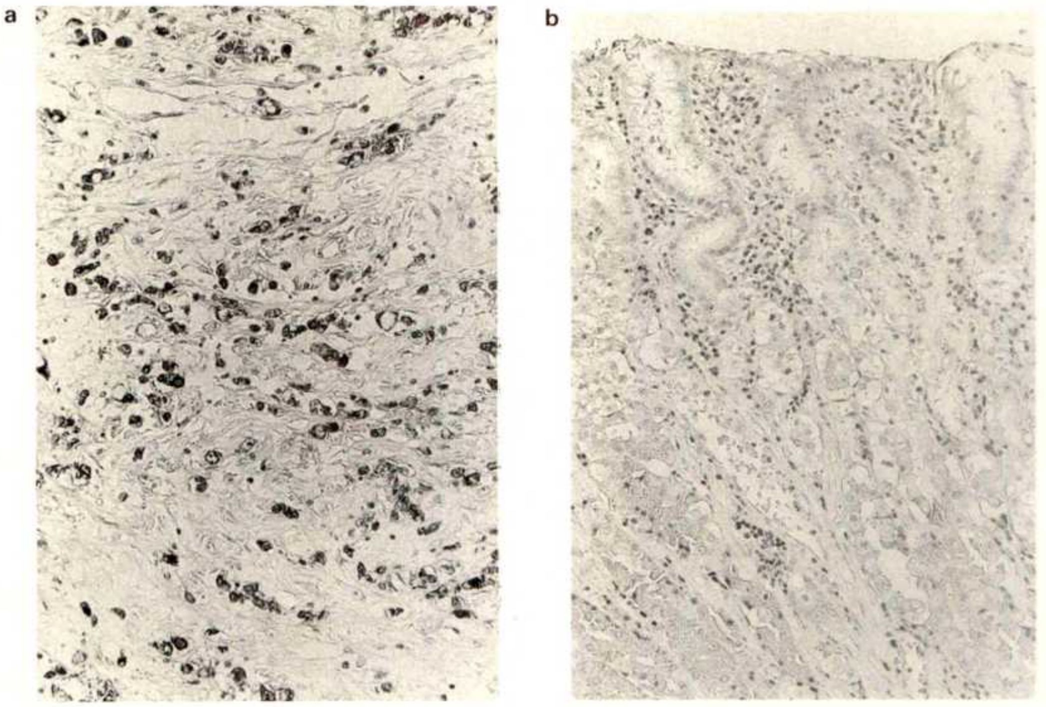

Figure 1 **a** *Section of scirrhous gastric carcinoma revealing strong, diffuse staining by monoclonal antibody S202.* **b** *Section of normal stomach showing no staining except for the apical surface of the superficial epithelial cells of normal mucosa which are slightly stained in some cases. Immunoperoxidase on paraffin section counterstained with haematoxylin. Original magnification × 100*

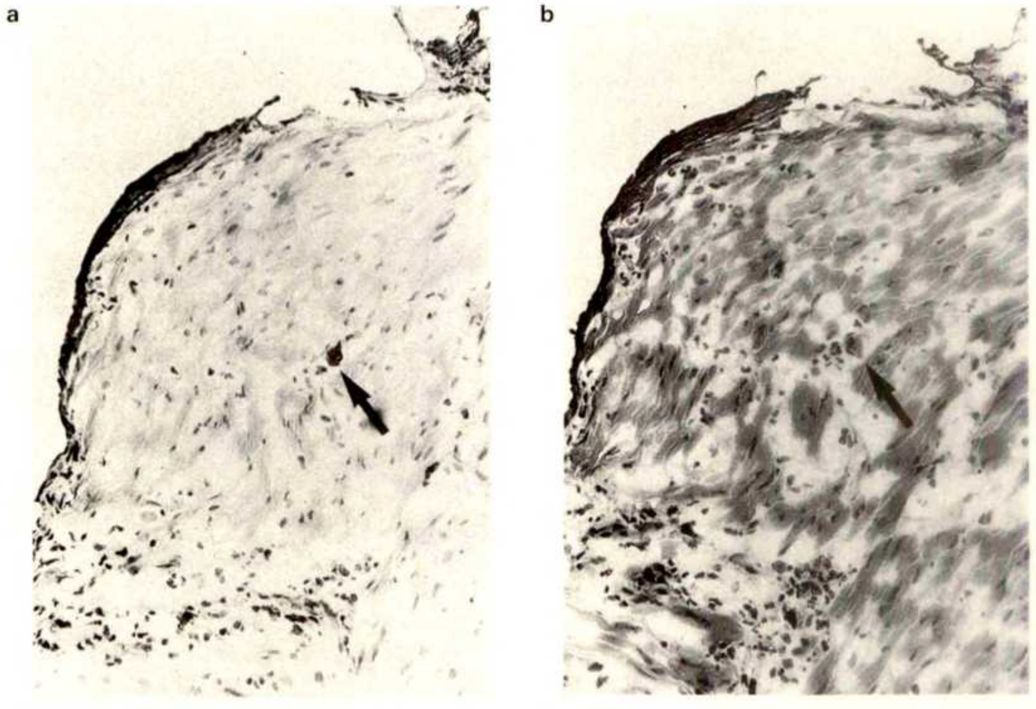

Figure 2 **a** *Scirrhous carcinoma cells stained by the rapid immunostaining method and* **b** *by haematoxylin and eosin stain. The single tumour cells at the surgical margin are clearly distinguished from the inflammatory cells by the immunostaining method (arrow). Original magnification × 100*

Discussion

At the time of surgery, it is important to detect whether the resected margin contains carcinoma cells, but it is difficult to identify scirrhous carcinoma cells of Borrmann type 4 microscopically, as disseminated tumour cells extend through the gastric wall without forming a definite malignant focus. As there is a high risk of leaving tumour cells at the resection margin, accurate detection of these cells is of therapeutic and prognostic importance.

We applied MAb S202, which strongly reacted with gastric carcinoma cells but not with inflammatory cells, to determine the limit of cancer invasion at the surgical margin of Borrmann type 4 gastric cancer during surgery. The ability to discriminate between carcinoma cells and inflammatory cells by the use of rapid immunostaining with MAb S202 was demonstrated on cryostat sections of tumour tissues. In this series, two cases were detected by the immunostaining method, while in a third case further resection was performed on the basis of positive immunostaining, in the presence of an inconclusive haematoxylin and eosin examination. Although adenocarcinoma cells were detected, and were suspected in one case, on cytological criteria, staining of these sections by the antibody resolved all suspicion.

The majority of scirrhous gastric carcinomas are formed by the infiltration of poorly differentiated adenocarcinoma cells that contain a small amount of mucin[1], whereas the percentage of mucin-containing signet-ring-cell carcinomas that invade beyond the submucosal layer is only 6 per cent of all scirrhous carcinomas[3]. Therefore, mucin-staining dyes are not useful for detecting malignant cells that invade beyond the resection margin. Because the MAb S202 reacted with nearly all adenocarcinomas[5], it appears reliable for detecting scirrhous carcinoma cells in a resected specimen.

Recently, several studies have reported the application of immunohistochemical techniques to supplement the diagnostic information obtained by conventional cytomorphology[8–20]. Previous reports[5] highlight some discrepancies in the histological findings of the immunoperoxidase and haematoxylin and eosin staining methods with respect to the depth of stomach tumour invasion. The invasive carcinoma cells could be detected more clearly by immunohistochemical staining with MAb S202 than by histological staining with haematoxylin and eosin. Thus, the reactivity of this antibody with scirrhous gastric carcinoma cells, but not with inflammatory cells, makes it a useful diagnostic tool.

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Role of cholecystostomy in the management of critically ill patients suffering from acute cholecystitis

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Between the years 1976 and 1985, 60 patients underwent cholecystostomy for acute cholecystitis in the surgical department of the Rokach hospital in Tel Aviv. The patients' average age was 73 years; 78 per cent were 70 years or older at the time of operation. The decision to perform cholecystostomy was taken before the operation which was performed as an emergency procedure for patients considered to be at high risk for cholecystectomy. Forty-six patients (77 per cent) had severe concomitant diseases, and 42 per cent of them had two or more associated diseases simultaneously. The cardiac risk index was high in most patients (90 per cent). Fifty-two patients recovered promptly after surgery. Five patients (8 per cent) developed significant postoperative complications. Three other patients (5 per cent) died of cardiovascular complications. Forty-two patients (70 per cent) underwent an elective cholecystectomy 6–8 weeks later with no further morbidity or mortality. Eleven patients who were at high risk had no further surgery. No residual stones were found in these patients and no relapse of the disease was recorded in the long term follow-up. Four patients were lost to follow-up. We conclude that cholecystostomy may still be used as an initial life saving procedure for critically ill patients with acute cholecystitis, and serves as a definitive procedure for patients considered to be at very high operative risk and who have no residual stones.

Keywords: Acute cholecystitis, cholecystostomy, surgical treatment

Acute cholecystitis among the elderly and debilitated may have a hazardous and atypical course[1,2]. Aggravation of systemic concomitant diseases may predominate in the clinical picture and the proper diagnosis is liable to be made late when the patients are already critically ill[2,3]. In order to prevent life threatening complications, prompt diagnosis and treatment are essential.

It is widely accepted that cholecystectomy is the procedure of choice for this condition[4]. The role of cholecystostomy in management is controversial. In the very ill patient with empyema of the gallbladder, severe concomitant disease or sepsis, cholecystectomy may carry a high operative risk. For these patients, a limited procedure might be warranted. Cholecystostomy is a short and simple procedure which could, therefore, be considered in such circumstances[4,5].

We report our experience with 60 patients who underwent cholecystostomy as an initial emergency procedure for acute cholecystitis.

Patients and methods

Five hundred and eight patients with acute cholecystitis were treated in the surgical department of the Rokach Hospital in Tel Aviv, during the 10-year period 1976–85. Sixty of these patients (11·8 per cent) underwent cholecystostomy as the initial treatment and their records were reviewed retrospectively.

There were 32 men and 28 women patients. The mean age was 73 years, with 78 per cent of patients being 70 years or older (*Figure 1*). The mean duration of symptoms before admission was 23 h (range from 6 h to 3 days). Patients were operated on within 5–26 h (mean 8 h) of hospitalization.

Diagnosis

Fever was the most common presenting sign (found in 66 per cent of the patients); this was followed by local tenderness and guarding (45 per cent), right upper quadrant mass (18 per cent), and jaundice (16 per cent). Right upper abdominal pain was the most prevalent symptom (60 per cent). Six patients were considered to be in septic shock on admission, as manifested by hypotension, oliguria and peripheral vasoconstriction. The white blood cell count was elevated in 57 per cent of the patients.

In 25 patients (42 per cent), cholelithiasis or past history of recurrent cholecystitis was obtained. In 27 patients (45 per cent) further investigation to confirm the diagnosis was necessary. Until 1979 intravenous cholangiography was the diagnostic procedure of choice in our hospital. It was performed in 18 patients. From 1979 ultrasonographic examination was used and was performed in nine of the patients. In eight patients, in whom the diagnosis was based on the clinical picture only, rapid deterioration mandated emergency intervention and precluded further diagnostic workup.

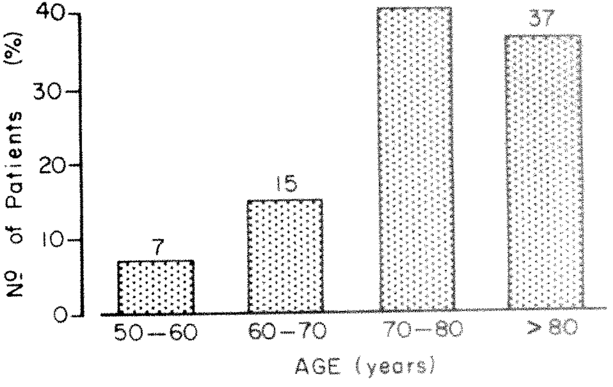

Figure 1 *Age distribution in 60 patients who underwent cholecystostomy (figures over each column refer to percentage of total patient series)*

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Table 1 *Clinical details of patients who died postoperatively*

Patient	Age (years)	Concomitant diseases	Clinical symptoms and signs	Causes of death
1	81	Insulin dependent diabetes mellitus Congestive heart failure	Peritonitis Septic shock Congestive heart failure	Acute myocardial infarction
2	78	Non-insulin dependent diabetes mellitus Ischaemic heart disease	Local peritonitis Complete A–V block (pacemaker insertion)	Congestive heart failure Respiratory failure
3	90	Ischaemic heart disease Congestive heart failure	Fever – 38·0 Right upper quadrant mass Local peritonitis	Sepsis Arrhythmia

Assessment of operative risk

Most patients (77 per cent) had suffered from severe concomitant diseases, contributing significantly to their operative risk. Ischaemic heart disease, presenting as congestive heart failure, recent myocardial infarction, or significant arrhythmia was found in 33 patients. Thirteen patients were bedridden owing to neurological disorders, such as hemiplegia or paresis. Eleven patients had chronic obstructive pulmonary disease, and nine suffered from chronic renal failure. Forty-two per cent suffered from a combination of two or more concomitant diseases.

Computation of the cardiac risk index according to Goldman *et al.*[6] showed that 54 patients (90 per cent) were in risk classes 3–4, which represents a high probability for fatal outcome or life threatening complications.

Operative treatment

The decision to perform a cholecystostomy was taken before operation and was based on the patient's clinical condition, assisted by knowledge of the estimated cardiac risk index[6].

Forty-three patients (72 per cent) were operated on under general anaesthesia, while the rest were operated on under local or regional anaesthesia. A right subcostal incision was used. An empyematous gallbladder was found in 53 patients. In the remaining seven, the gallbladder was already perforated with walling off by the greater omentum. Cholelithiasis (either single stone, multiple stones or 'sludge') was found in 57 patients. Three patients had acalculus cholecystitis.

The gallbladder was drained and the stones evacuated. A large bore rubber catheter was introduced into the gallbladder and drawn through a separate skin incision. The mean operation time was 20 min (range 15–30 min).

Results

Fifty-two patients showed rapid clinical improvement within 24 h. The presenting symptoms were alleviated and mental, cardiovascular and pulmonary function were stabilized. These patientls had an uneventful recovery with a mean hospital stay of 7·6 days.

Three patients (5 per cent) died within 30 days of operation (*Table 1*). All were older than 78 years, had significant concomitant diseases, and were admitted to the hospital in severe clinical condition. In these three patients death was attributable to cardiopulmonary complications. It is noteworthy that one patient refused surgery for 4 days, and was operated on in a state of septic shock (patient No. 3, *Table 1*).

Five other patients (8 per cent) had significant postoperative complications. Two patients who had unstable angina developed acute myocardial infarction. Acute renal failure occurred in two patients who had been in septic shock. The fifth patient developed a rectus sheath haematoma which was treated surgically. These patients recovered promptly with a mean hospital stay of 14·7 days.

Follow-up

Forty-two patients (70 per cent) underwent an elective cholecystectomy, 6–10 weeks after the first procedure. There were no deaths or major complications among these patients.

In 15 patients, cholecystectomy was not carried out. Cholangiograms performed through the draining tube revealed no residual stones in 11 patients. These were high risk patients with severe cardiovascular diseases and all were over the age of 79 years. The drains were removed and the patients were followed in our outpatient clinic for 1–6 years. During this period no recurrence of acute cholecystitis was detected. Four patients were lost to follow-up.

Discussion

It is generally accepted that medical therapy is ineffective in acute cholecystitis, and surgical intervention is advocated[7,8]. Diagnostic procedures should be undertaken while the patients are being prepared for surgery. Treatment of concomitant disease, correction of fluid and electrolyte imbalance, and antibiotics should be commenced. The appropriate surgical approach should then be decided upon. Recently, some authors have advocated the use of percutaneous cholecystostomy as an initial drainage technique[9–11]. The procedure has been performed in a limited number of patients and has not yet gained wide acceptance. Cholecystectomy is the ultimate solution for acute cholecystitis[12]. Many surgeons would perform cholecystostomy only when cholecystectomy is impossible owing to technical or other intraoperative difficulties[8,13]. The decision to terminate the operation with cholecystostomy under these circumstances is usually taken after extensive manipulations in a high risk patient. It seems, therefore, that to advocate cholecystectomy for all patients with acute cholecystitis might be too hazardous. Indeed the results of urgent cholecystectomy have not always been encouraging with mortality rates of up to 10 per cent and morbidity rates of up to 40 per cent[2,14,15] in the subgroup of patients over the age of 70 years.

In this report a different therapeutic approach was presented. Sixty (11·8 per cent) of 508 patients with acute cholecystitis were evaluated as being at high risk for cholecystectomy. In these high risk elderly patients with severe concomitant diseases, a short life saving procedure, namely cholecystostomy, was performed. The decision was taken before surgery, and thus a short general or regional anaesthesia and limited incision were planned. This approach minimized the operative trauma, spared the possibility of a long troublesome operation, and ensured adequate drainage of the inflamed gallbladder. The results were encouraging with low mortality (5 per cent) and morbidity (8 per cent) rates. Although this approach necessitates subsequent operation, cholecystectomy performed in 74 per cent of the survivors resulted in no mortality and only minor morbidity. Therefore the need for a second definitive operation should not be an argument against performing cholecystostomy as an initial procedure. Moreover, in eleven patients (19 per cent of the survivors) cholecystectomy was not performed because the cholangiogram showed no residual stones and the patients were still in a poor general condition and at too high an operative risk. We assume that emergency, or delayed elective cholecystectomy, in these 11 patients would have resulted in a higher rate of mortality. Frequent ambulatory observation revealed that none of our patients developed symptoms or signs of acute cholecystitis. These findings are in accordance with those of Ellis[4] who suggested that cholecystectomy should not be attempted in all patients.

As life expectancy is increasing and the incidence of gallstones increases with age[1,2], it is anticipated that a larger number of elderly high risk patients will suffer from acute cholecystitis[16]. Cholecystectomy in the elderly, critically ill patient, although the preferred treatment, carries a high risk of complications. Therefore, there is still a role for cholecystostomy in treating these patients.

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Surgical significance of the bile duct of Luschka

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In 20 post-mortem dissections, the subvesical bile duct of Luschka was noted in six specimens. Microscopic examination of ten other post-mortem gallbladders revealed small bile ducts on the gallbladder surface in five. Four cases of injury to the duct of Luschka during cholecystectomy are described and illustrated with cholangiographic and histological evidence. Post-cholecystectomy bile leaks from the drain tube, which closed spontaneously without sequelae, were noted in 9 per cent of 204 randomly selected cases and were regarded, at least in some, as being caused by a divided duct of Luschka. The practical significance of this duct during cholecystectomy is to keep close to the gallbladder wall during removal of the gallbladder, and to ligate a divided bile duct of Luschka if recognized at surgery.

Keywords: Cholecystectomy, bile ducts, anatomy, subvesical duct, duct of Luschka, biliary fistula

In 1863 Luschka[1] first described a slender bile duct passing from the right lobe of the liver in the gallbladder fossa and joining the right hepatic or common hepatic duct. Most workers have described this duct as a structure 1–2 mm in diameter which drains a variably sized subsegment of the posterior segment of the right liver lobe to empty into the right hepatic, common hepatic or, rarely, the cystic duct[2–8]. The reported incidence of this duct varies from 1 per cent[8,9] to 50 per cent[2,5]. The importance of the duct lies in its vulnerable position during cholecystectomy. The frequency of damage to the duct is not known and the techniques for avoiding or recognizing its injury have not been previously emphasized.

Materials and methods

The duct of Luschka and damage to it were studied by three methods: post-mortem dissections, operative cases and post-cholecystectomy bile leakage.

Post-mortem dissections

A series of 30 post-mortem dissections were performed. In 20, gross dissections were made with special attention being paid to the gallbladder bed and the cholecystohepatic triangle of Calot. In another ten post-mortems, three tissue blocks were taken from the undisturbed gallbladder bed and embedded in paraffin; 5-μm sections were cut, stained with haematoxylin and eosin, and examined microscopically by two independent observers.

Operative cases

Four cases of damage to the duct of Luschka during cholecystectomy which came under the care of the authors over a 12-month period were studied.

Post-cholecystectomy bile leakage

The case notes of 204 patients who underwent cholecystectomy at the Repatriation General Hospital, Heidelberg, from 1985 to 1987 were examined for evidence of a postoperative bile leak, its duration and the quantity of bile drained through the drain tube.

Results

Post-mortem dissections

Only cases without previous biliary disease were selected for examination. Twenty gross post-mortem dissections were performed. There were six subvesical ducts found (30 per cent). Five of these were placed fairly centrally within the gallbladder bed and one was in the lateral peritoneal reflection (*Figure 1*). Five of the ducts were traced to the right hepatic duct, while the sixth entered the common hepatic duct. None entered the cystic duct.

In none of these was the duct seen before dissection of the gallbladder from its bed. With standard surgical technique, remaining close to the gallbladder wall, there was no incidence of transection of the duct. Histological examination of one of these specimens showed that it was a meshwork of tiny ductules rather than a single duct.

A further series of ten post-mortem specimens was subjected to histological examination after sectioning the undissected gallbladder bed. In five of these cases, microscopic bile ducts were identified on the surface of the liver or in the adipose tissue of the gallbladder bed. They occurred either as single ducts or as groups of tiny ducts (*Figure 2*).

Operative cases

Case 1. A 47-year-old woman presented with a 2-day history strongly suggestive of acute cholecystitis. The liver function tests showed a mild obstructive picture. At operation, a distended, acutely inflamed gallbladder was found and decompressed. Calot's triangle was dissected and the cystic artery divided. The gallbladder was dissected from its bed close to the wall and an operative cholangiogram was performed (*Figure 3*). The gallbladder was removed, revealing a severed duct in its bed which was less than 1 mm in diameter. There was a significant leak of bile which was stopped by the application of a single metal clip. The leak of contrast medium

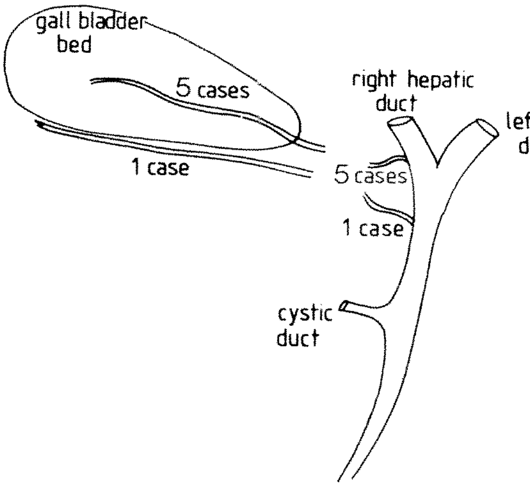

Figure 1 *Diagram of the sites of the subvesical duct in the gallbladder bed and the sites of termination in 20 post-mortem dissections*

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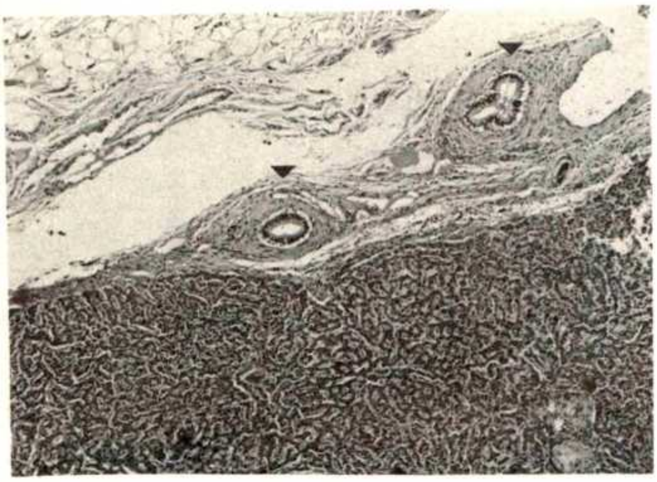

Figure 2 *Section of the gallbladder bed showing fine bile ducts applied to the capsule of the liver and shown by arrows. (Haematoxylin and eosin, original magnification × 40)*

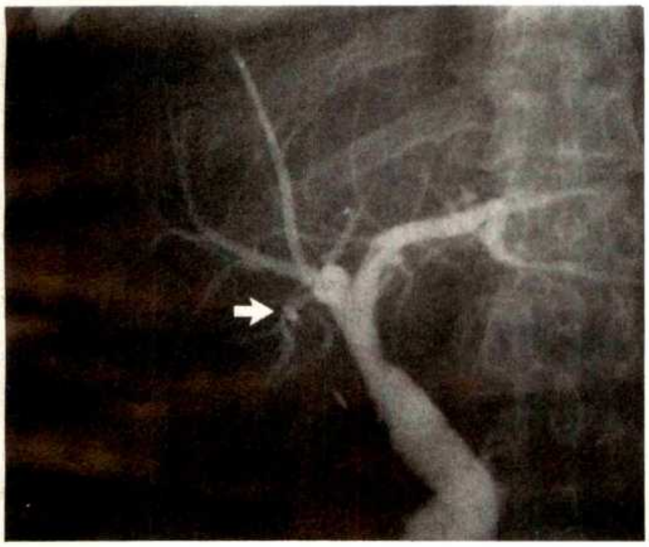

Figure 3 *Case 1. Operative cholangiogram showing extravasation of contrast medium from the divided duct of Luschka (arrow)*

from this duct was apparent on the cholangiogram. Postoperatively, there were no complications and, in particular, no bile leak was evident. The drain tube was removed on the second day. The liver function tests improved immediately postoperatively. Histological examination of the gallbladder demonstrated that the small divided duct was intimately associated with the muscular wall but did not enter the lumen of the organ (*Figure 4*).

Case 2. A 59-year-old woman had an elective cholecystectomy for gallstones. At operation, a mucocele of the gallbladder was found with a stone impacted in Hartmann's pouch. A routine dissection of Calot's triangle and the gallbladder was performed during which a subvesical duct of less than 1 mm diameter was found in the interior reflections of the peritoneum. This was ligated at its proximal and distal ends. No operative cholangiogram was performed. Postoperatively there was no bile leak. The drain tube was removed on the second day and the patient made an uneventful recovery.

Case 3. A 24-year-old woman underwent elective cholecystectomy for gallstones. At operation, a short cystic duct was found which entered the right hepatic duct. An operative cholangiogram was performed, and the gallbladder was dissected from its bed. During this dissection, a fine subvesical duct was seen in the inferior peritoneal reflection and was ligated with metal clips. The duct was not visible on the cholangiogram, even in retrospect. Postoperatively, there was no bile drainage through the drain tube which was removed on the second day, and the patient made an uneventful recovery.

Case 4. A 53-year-old woman underwent elective cholecystectomy for a solitary gallstone. The gallbladder, which was somewhat embedded in the liver, was removed by sharp dissection close to the gallbladder wall. No cholangiogram was performed. On removal of the gallbladder, a tiny duct was seen in the inferior leaf of the peritoneal reflection, and it was leaking bile. This was ligated with a Dexon® (Davis and Geck, Gosport, UK) suture. Postoperatively, there was a leakage of 200 ml of bile in the first 36 h. This leakage then ceased and the tube was removed on the third day. There were no other complications and the patient was discharged on the sixth postoperative day.

Cholecystectomy series

In the 2-year period 1985–87, there were 318 cholecystectomies performed at this hospital. Of these, 204 cases were randomly selected. In these cases, cholecystectomy was performed without exploration of the common duct. There were eight cases (4 per cent) where no postoperative drains were used. A bile leak, defined as the presence of bile in the drain fluid reported in the case notes postoperatively, was seen in 19 cases (9 per cent). In these patients, the drain tube remained in place for an average of 6 days, with a range of 3–23 days. The amount of fluid drained ranged from 100 to 2000 ml with a mean of 740 ml. The amount of fluid drained per day ranged from 30 to 270 ml, with a mean of 120 ml per day. In all cases, bile leakage stopped and there were no persistent biliary fistulae. In one of these cases (0·5 per cent), a second procedure was required to drain a bile collection. At operation, the source of the leak could not be identified.

Discussion

The dissections have confirmed the occurrence of the duct of Luschka in a substantial number of cases. This is also the first report of the 'duct' occurring in the form of a meshwork or leash of tiny ductules. Also, microscopic bile ducts were found distributed within the connective tissue of the gallbladder bed, as has been described for subserosal ducts in other sites[4]. The duct was found to occur at two main sites in the gallbladder bed, most commonly in the centre of the bed but also in the lateral peritoneal reflection. In none of the post-mortem dissections was the duct visible before dissection of the gallbladder from its bed. All these features make its surgical

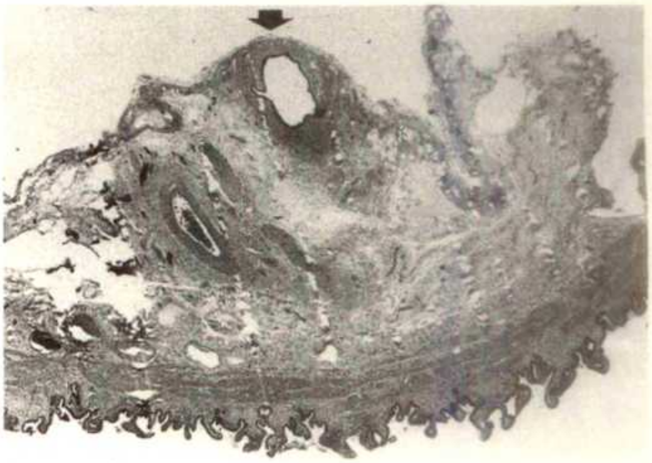

Figure 4 *Case 1. Section of the gallbladder wall and its bed with the duct of Luschka shown by an arrow. (Haematoxylin and eosin, original magnification × 10)*

identification difficult, and our clinical experience with operative cholangiography was generally not rewarding in identifying the duct.

There are differing opinions about whether the intrahepatic area drained by the duct has alternative routes of drainage or whether there are no intersubsegmental communications[4,6,8]. It is not proved, but it is the belief of the authors that intercommunications do exist, as all damaged subvesical ducts stop draining bile spontaneously without sequelae, whereas damaged major bile ducts may not[2,10].

The surgical significance of injuring the duct lies in the production of a bile leak. Several recent studies[11–13] have suggested that the incidence of fluid collections is not affected by the presence of a drain and that drain tubes promote other complications, such as pulmonary atelectasis and wound infection. However, these studies involved quite small numbers. Hoffman and Lorentzen[14] have made an extensive review of the literature and in 8423 cases found a slightly higher incidence of bile collections in the drained group (0·66 per cent) than in the non-drained group (0·27 per cent), but they were unable to exclude selection bias. They also point out that most studies report the incidence of 'fluid drainage' and the true incidence of bile in that fluid is uncertain. We have taken care in our retrospective review of operative cases to include only those cases where a definite leakage of bile has been observed by medical staff. The incidence of postoperative bile leakage in the present series was, surprisingly, not small (9 per cent). Our series cannot identify which of the leaks were due to a severed subvesical duct. However, it is the belief of Kune[2] that a sloughed or slipped ligature on the cystic duct is a rare event, so it seems reasonable to presume that at least a proportion of these leaks were due to a severed duct of Luschka.

The cases reported here also demonstrate that if the injury is recognized and dealt with at the time of operation, then the risk of bile leakage is minimal and postoperative recovery is normal. Some authors have reported repairing ducts of this size[9] in the belief that this maintains function in the drained area of liver. The authors believe this to be unnecessary and advise simple ligation. To avoid damaging the duct, it is recommended that the surgeon remain close to the gallbladder wall during its removal. However, in one of the reported cases (case 1) the duct was so intimately related to the wall that even the most meticulous technique could not have avoided its division. This strengthens the case for routine postoperative drainage after cholecystectomy.

In conclusion, the surgical significance of the duct of Luschka is firstly to recognize and prevent injury by keeping close to the gallbladder wall during cholecystectomy, and secondly to under-run or ligate the ends if an accidental division of the duct is recognized.

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Changes in vascularity of liver tumours after hepatic arterial embolization with degradable starch microspheres

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The role of vascularity as a prognostic factor was investigated in 35 patients undergoing arterial chemotherapy for liver tumours. Compared with parenchyma, tumour vascularity was classified as hot (18 cases), cold (12 cases), and mixed (12 cases) using ^{99m}Tc-macroaggregated albumin (MAA) hepatic arterial scans. The proportion of patients showing complete and partial responses to treatment was higher in the hot group (56 per cent) than in the combined cold and mixed group (12 per cent). In 15 cases (six hot, six cold and three mixed lesions), additional MAA scans were performed immediately after arterial embolization with degradable starch microspheres (DSMs). Either complete or partial reversal of tumour vascularity was observed after DSM-embolization in five and seven cases respectively, two and two of them respectively showing native cold lesions. As tumour vascularity appears to be a prominent prognostic factor, DSM-embolization should improve the efficacy of treatment by improving liver extraction of drugs and causing flow redistribution towards hypovascular areas.

Keywords: Liver neoplasms, drug therapy, radionuclide imaging, surgery, liver circulation, microspheres

Both animal and human studies have demonstrated that liver tumours, unlike liver parenchyma, are supplied mainly by the hepatic artery[1,2]. Thus, the arterial route is generally thought to be the most valuable single access for regional treatment of liver tumours. Higher concentrations of drugs should be achieved in the tumour than in the parenchyma and systemic toxicity should be reduced due to the first pass extraction.

A great variability of flow patterns, however, is a characteristic of tumour circulation[1,3]. Consequently, tumour masses can have either 'hypervascular' (hot) or 'hypovascular' (cold) appearances as evaluated by both standard arteriograms[4] and ^{99m}Tc-macroaggregated albumin (MAA) hepatic artery perfusion scans[5–9]. These appear to reflect the respective arterial flow and the flow-related drug distribution to the tumour and to the parenchyma. Indeed, tumour vascularity has been identified as a prominent prognostic factor in regional chemotherapy of liver tumours[4–9]. Thus manipulation of intrahepatic arterial flow should be useful in increasing the regional advantage of intra-arterial chemotherapy, particularly in cold masses. For this purpose, vasoactive drugs[10], degradable starch microspheres (DSMs)[11,12] or drug-loaded microspheres[13] can be employed.

DSMs (Pharmacia AB, Uppsala, Sweden) consist of glucose polymers cross-linked with epichlorohydrine bridges to form spheres with a mean (s.d.) diameter of 40(5) μm, being degraded by serum α-amylases with a $t_{\frac{1}{2}}$ of 15–30 min at 37°C *in vitro*. Once injected into an artery, they block flow at the arteriolar–capillary level, but this is fully reversible even after repeated administration[14]. During degradation, they maintain their size and shape until they finally collapse, allowing the blood flow to recommence[15]. DSMs have been used to slow blood flow in several organs, including small bowel, kidney, and liver[11,12]. The administration of 90×10^6 parts of DSMs into the hepatic artery proper reduces the arterial blood flow by approximately 80 per cent[16]. Consequently, the short-lasting slow-down of arterial flow following a single bolus injection of DSMs into the hepatic artery has been used to improve the extraction of a concurrently infused drug by the liver as a whole, and to reduce systemic toxicity. A reduced systemic spill-over owing to increased uptake by the liver has been demonstrated for 5-fluorouracil (5-FU)[15,17], mitomycin C[18,19], carmustine[16], and doxorubicin[20].

As DSMs have a tendency to go preferentially to high flow areas[21], the arteriolar capillary blockade should prevail in these areas, thus producing an increased arterial back pressure that would forcibly redistribute the residual arterial flow towards previously ischaemic areas. The present report assesses the possibility of modifying tumour vascularity by distal embolization of the hepatic artery with DSMs.

Patients and methods

Thirty-five patients undergoing intra-arterial chemotherapy for biopsy-proved liver tumours were investigated. The study was carried out in all cases according to the ethical standards of the Committee of Human Experimentation of our Institute. There were 22 men and 13 women, with a median age of 62 years (range 44–75 years) and median performance status of 1 (Eastern Co-operative Oncology Group: ECOG). Thirty-one patients had colorectal liver metastases and four had primary liver tumours (three hepatocarcinomas and one cholangiocarcinoma). A complete staging was carried out routinely, including: blood and urine examinations, abdominal computed tomographic (CT) scan, plain chest X-ray, superselective arteriogram, ^{99m}Tc-sulphur colloid scan, and ^{99m}Tc-macroaggregated albumin (MAA) angioscintiscan. All cases in this report had normal hepatic arterial anatomy and detectable liver tumours by MAA, sulphur colloid and CT scanning. The degree of liver replacement, as demonstrated by CT scan, was lower than 25 per cent in seven cases, between 25 and 50 per cent in 18, and higher than 50 per cent in ten. Regional access was obtained surgically with either Infusaid-400 pumps (Infusaid Incorporated, Norwood, Massachusetts, USA) or implantable ports, the catheter being inserted into the gastroduodenal artery up to its ostium[22]. The gallbladder was removed, and all vessels downstream of the catheter were interrupted.

A hepatic artery perfusion scan was performed in all cases shortly after the operation using 5 mCi MAA infused through the arterial catheter at a flow rate of 0·1 ml/s (3 ml). The catheter was then flushed at the same flow rate with 3 ml heparinized saline. Imaging was accomplished with a wide-field-of-view, single-crystal γ camera with a low energy, general purpose, parallel hole collimator. The camera was placed to include the liver and lungs excluding lung apices. After the dynamic study, the anterior, posterior, and lateral views of the abdomen and lungs were acquired with a Digital computer PDP 11/34, collecting

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Table 1 *Relationships between tumour vascularity, degree of liver replacement, and tumour response in the 35 cases*

	Liver replacement as demonstrated by CT scan								
	Hypervascular			Mixed			Hypovascular		
Liver responses to chemotherapy	<25	25–50	>50	<25	25–50	>50	<25	25–50	>50
Complete response	1	—	1	—	—	—	—	—	—
Partial response	3	4*	1	—	1	—	—	1	—
Minor response	1	1	—	—	2	1*	—	1	—
Stable disease	1	2	1	1	—	—	—	1	1
Progressive disease	—	1	1	—	—	—	—	3*	5*

* One primary tumour; CT, computed tomographic

500000 counts on a matrix 128×128. Images were visually inspected by two experienced nuclear medicine specialists and compared with the conventional ^{99m}Tc-sulphur colloid scan. Indeed, even in comparison with computer assisted study of bidimensional regions of interest, visual inspection of the three projections appeared to give the best evaluation of vascularity in limited areas of the liver after MAA scans[7,9]. The distribution of MAA in the obvious tumour masses was classified as 'hot' (hypervascular) or 'cold' (hypovascular) when tumour uptake was compared with that of normal parenchyma. Tumours were classified as of 'mixed' type when there was gross coexistence of the two vascular patterns. Finally, images were inspected visually to identify any significant uptake in the lungs. These determinations were made without knowledge of the patient's clinical data.

Additional perfusion scans were performed in 15 patients 2–7 days after the first perfusion scan had shown hypervascular, hypovascular and mixed patterns in six, six, and three cases respectively. They were carried out with the above mentioned schedule immediately after infusing from 45×10^6 to 90×10^6 parts of DSMs through the arterial catheter. The total amount of microspheres was suspended in 50 ml of normal saline and, to avoid sedimentation, the syringe containing the mixture was shaken for 30 s before, and continuously during, the injection. Liver enzymes were monitored after DSM-administration. The differential patterns of vascularity in the obvious tumour masses were noted in each patient and the individual changes were attributed to the arterial flow redistribution caused by distal embolization with DSMs.

The cases evaluated in this report were studied during consecutive prospective phase II multicentre trials. Chemotherapy regimens were as follows: (1) continuous intra-arterial 5-fluor-2'deoxyuridine (FUdr), 0·3 mg/kg per day, from day 1 to 14 every 28 days (nine colorectal, one hepatoma); (2) bolus intra-arterial epirubicin, 30 mg, day 1 every 7 days (ten colorectal, two hepatoma, one cholangiocarcinoma); (3) bolus intra-arterial cisplatin, 40 mg/m^2 per day, from day 1 to 3 every 21 days + bolus intravenous 5-FU, 200 mg/m^2 per day, from day 1 to 5 every 21 days (seven colorectal); (4) continuous intra-arterial 5-FU, 20 mg/kg per day, from day 1 to 5 every 28 days (two colorectal); (5) continuous intra-arterial and intraportal 5-FU, 500 mg/m^2 per day, from day 1 to 5 every 28 days + bolus intra-arterial and intraportal mitomycin C, 10 mg/m^2, day 1 every 28 days (three colorectal). Due to the relative heterogeneity of clinical material, the prognostic value of MAA scanning on survival times has not been considered. However, as the proportions of both responses and vascularity patterns appeared well balanced in the different treatment groups, the relationship between vascularity and responses was analysed.

The liver responses to chemotherapy were evaluated by CT and/or echoscans every second month. The evaluation of the single lesions was made by surface area approximation, multiplying the longest diameter by the greatest longitudinal diameter. In the case of multiple lesions the products of the diameters of all lesions were summed. Complete response, partial response, minor response, stable disease, and progressive disease were designated as follows: complete response, disappearance of all known disease, as determined by two observations; partial response, a 50 per cent or greater decrease in total tumour size of the known lesions, as determined by two observations and no appearance of new lesions or progression of any lesion; minor response, 25–49 per cent reduction of tumour size without appearance of new lesions or progression of any lesion, as determined by two observations; stable disease, a less than 25 per cent decrease in total tumour size cannot be established or less than 25 per cent increase in the size of one or more measurable lesions; progressive disease, a 25 per cent or greater increase in the size of one or more measurable lesions, or the appearance of new lesions.

To determine whether the proportions of responders and non-responders among those patients with hot, cold or mixed vascular patterns were similar, patients were analysed in two-by-two tables with the two-tailed Fisher's exact probability test.

Results

Table 1 reports the number of therapeutic responses in the 35 patients matched with the degree of liver replacement and tumour vascularity, as evaluated by MAA perfusion scan. Owing to the small number of personal cases studied in each of the co-operative chemotherapy trials (the number of cases being 10, 13, 7, 2, and 3), the results of the various treatments are reported together. Indeed, the overall response rates of colorectal liver metastases in three of the above mentioned co-operative trials (National Register of Implantable Systems, unpublished data) were 38 per cent with FUdr (treatment (1), 71 cases overall), 36 per cent with epirubicin (treatment (2), 22 cases), and 47 per cent with cisplatin + 5-FU (treatment (3), 44 cases). In the different treatment groups, the proportion of pretreated cases and vascular patterns appeared well balanced, and similar response rates were shown by both colorectal metastases and primary tumours.

The simple pretreatment MAA perfusion scan showed hot, cold and mixed patterns in 18, 12 and five patients respectively. The frequency of complete + partial responses was significantly higher ($\alpha < 0{\cdot}05$) in the hypervascular than in the hypovascular group ($P = 0{\cdot}02$). Significant differences in response (complete + partial responses) were also observed when mixed cases were added to either group ($P = 0{\cdot}042$, or $P = 0{\cdot}016$ respectively). When only colorectal metastases were considered, the frequency of responses, including minor responses, was significantly higher ($P = 0{\cdot}039$) in the hypervascular + mixed group (17 and four cases respectively) than in the hypovascular group (ten cases). Furthermore, both in the entire series and in patients with colorectal cancer, the hypervascular and mixed groups showed a higher frequency of patients with a liver replacement of less than 50 per cent. The response rate was also much higher in these cases.

Five patients undergoing DSM-embolization showed from WHO grade 1 (four cases) to 2 (one case) short-lasting elevations of liver enzymes. Six patients experienced mild to moderate short-lasting pain, while severe pain and vomiting occurred in two patients. Profound changes in liver perfusion, as evaluated by MAA arterial angioscanning, were observed in most cases after DSM-embolization (*Table 2*). In four cases, very limited portions of the organ were visible, suggesting an almost complete stoppage of arterial circulation. In two of them, reflux of tracer in the stomach and duodenum was observed, while a significant but subclinical pulmonary shunt was detected in one additional patient. Regarding arterial perfusion of tumour masses, compared with liver parenchyma, DSM-embolization induced a reversal of tumour vascularity patterns in two cases with hot masses and in two cases with cold masses at the previous examination. Mixed appearances were observed after DSM-administration in two and three cases which had previously shown cold and hot patterns respectively. Two of three cases showing mixed patterns at the first examination developed hot appearances, while a complete redistribution of tumour blood flow was seen in the third patient. The behaviour of such a case is illustrated in *Figure 1*.

Discussion

The low flow MAA arterial perfusion scan appears to give a useful and reproducible estimate of the relative arterial inflow to liver tumours and parenchyma[7–9]. Indeed, despite some minor differences in examination technique, the reported frequency of pure hypervascular lesions ranges between 58 and 60 per cent, with very similar figures (59–62 per cent) when only colorectal metastases are considered. As mentioned above, the obvious value of the examination is the identification of those cases able to take maximal regional advantage from intra-arterial chemotherapy.

The results of our study are consistent with the observations that tumour vascularity is a prominent prognostic factor in regional treatment of liver tumours[7–9]. The heterogeneity of our chemotherapy schedules is not likely to affect the results substantially, as similar response rates have been observed with the different treatments, both in our co-operative trials and in the literature[23]. In the report by Daly *et al.*[9], MAA scans provided a good positive correlation between tumour perfusion and treatment responses in 47 patients with colorectal liver metastases undergoing hepatic arterial infusion of FUdr. In addition, a trend ($P = 0{\cdot}08$) toward improved survival of the 'hypervascular' group was demonstrated. This suggests that in some patients the lack of response to treatment could be related to poor perfusion of either the entire tumour or portions of it. Only low concentrations of drug are likely to reach hypovascular areas, where 'dormant' cells could be responsible for subsequent disease progression.

Several patients in our series showed pure hypovascular lesions, while hypovascular and hypervascular areas coexisted in others. This variability of arterial flow patterns appears to reflect the irregular nature of tumour angiogenesis and its relationship with the dual vascular supply of the liver. As a rule, metastatic emboli and very small tumours are mainly nourished by portal blood whereas the arterial fraction of flow becomes predominant as tumour volume increases[1–3]. This is due to arterial hypervascularization of the proliferating peripheral ring, while hypovascularization, with ischaemia and perhaps necrosis, develops in central areas. Consequently, both

Table 2 *Changes in tumour perfusion, as evaluated with ^{99m}Tc-macroaggregated albumin arterial scanning, after arterial embolization with degradable starch microspheres*

	Primary tumours	Percentage liver replacement	DSM dose (mg)	Tumour perfusion	
				Without DSM	With DSM
1	Colorectal	25–50	900	cold	cold*
2	Colorectal	>50	900	cold	cold
3	Hepatocellular	>50	900	cold	mixed
4	Colorectal	>50	450	cold	mixed
5	Colorectal	25–50	900	cold	hot
6	Colorectal	25–50	450	cold	hot
7	Colorectal	25–50	900	mixed	mixed†
8	Colorectal	25–50	900	mixed	hot
9	Hepatocellular	>50	450	mixed	hot
10	Colorectal	>50	450	hot	hot
11	Colorectal	>50	900	hot	mixed
12	Hepatocellular	25–50	900	hot	mixed‡
13	Cholangiocellular	>50	900	hot	mixed
14	Colorectal	25–50	900	hot	cold
15	Colorectal	<25	900	hot	cold*

DSM, degradable starch microspheres; * reflux to splanchnic organs; † complete reversal of flow patterns; ‡ heavy shunt to the lungs

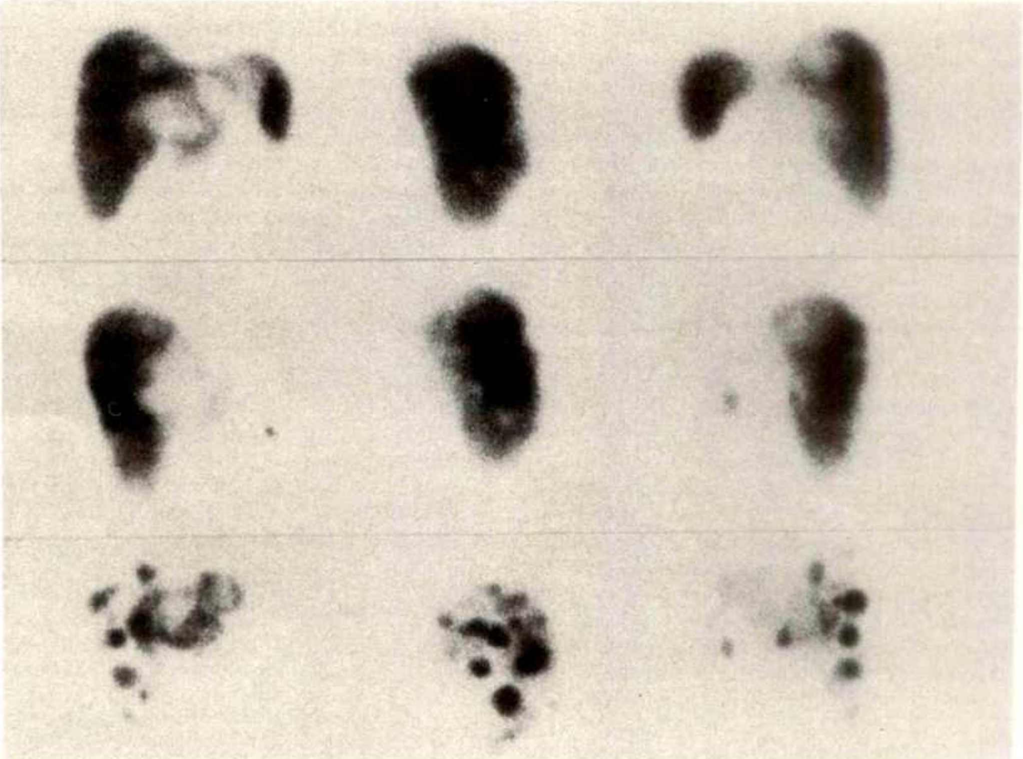

Figure 1 *A large lesion located in the left lobe and several smaller lesions located in the right lobe of the liver were identified with the sulphur colloid scan (top). They were classified as grossly hypovascular according to the first ^{99m}Tc-macroaggregated albumin (MAA) perfusion scan (middle). Compared with the parenchyma, a redistribution of flow towards all tumour areas is apparent in the second MAA scan, performed immediately after treatment with degradable starch microspheres (bottom). The relative residual hypoperfusion of the large mass, compared with the smaller ones, conforms to a substantial degree of central necrosis detected by ultrasound examination*

large and small tumours can have a very poor arterial inflow, and differential perfusion patterns can be demonstrated even in limited sections of central or peripheral areas of any kind of tumour. For this reason we established a category of 'mixed' lesions.

The lack of predictive value of the MAA perfusion test in non-responding patients with hypervascular masses may be explained, at least in part, by the relative inaccuracy of the examination. Even in the presence of hypervascular lesions, there may be hypovascular areas of the liver which cannot be shown by this kind of test. This assumption is supported by the results of CT examinations of metastasis-bearing livers using a new contrast medium (EOE-13) compared with MAA angioscan[24]. Finally, even the precise and complete definition of vascularity of the tumour cannot predict the subsequent vascularity of every single lesion; vascularity is known to undergo profound modifications with time, related to both the tumour growth and the effects of regional treatment[25].

The main purpose of our study was to investigate the possibility of manipulating intrahepatic arterial flow in man. Previous studies were performed in four patients with defective perfusion of an entire lobe of the liver after occlusion of aberrant hepatic arteries. After arterial embolization with DSMs, flow was redistributed towards the lobe supplied by the occluded artery in all cases[26]. The results of the present study, using low-flow MAA angioscanning, confirm preliminary observations with high-flow dynamic CT scanning[27]. In both cases a redistribution of flow towards hypovascular tumours can be shown after administration of DSMs in patients with normal hepatic arterial anatomy.

The induction of homogeneous perfusion of intrahepatic tumours appears to be of clinical value, as the changes induced by DSMs in tumour perfusion could increase drug uptake by the non-responsive hypovascular lesions. Although a direct correlation has been shown between tumour vascularity (MAA retention) and tumour FUdr levels during intra-arterial chemotherapy in humans[28,29], no data are yet available about the influence of DSM-embolization on changes in both perfusion and drug uptake of tumours showing different degrees of native vascularity.

The kinetics of anticancer drugs during DSM-administration have been extensively investigated in animals. Besides the increase of first pass extraction of drugs by the liver as a whole, DSM-embolization has been shown to increase not only tumour doxorubicin levels but also the tumour:parenchyma doxorubicin ratio when VX2 tumour is transplanted into rabbit hind leg[30] and liver[31]. This could be explained, at least in part, by a DSM-induced redistribution of flow to the tumour. However, as anthracyclines have a very high first pass extraction in the normal liver[32,33], the effect of DSMs could be related only to the DSM-induced slow down of arterial flow to the entire organ. Even in those cases in which DSM-embolization does not provoke changes in tumour vascularity, the first pass extraction could be increased to a greater extent in the tumour than in the parenchyma. This phenomenon could be magnified by a substantial washout of normal parenchyma owing to the portal flow. Therefore, when drugs are given mixed with DSMs in man, it seems important to correlate tumour uptake and responses not only to native vascularity but also to the changes in relative tumour perfusion induced by the microspheres themselves.

Our results indicate that distal arterial embolization with standard dosages of DSMs can be effective in redistributing arterial flow from previously 'hypervascular' towards previously 'hypovascular' areas. This phenomenon, however, has been observed only in a proportion of cases and, in some cases, only limited areas of cold lesions showed a change of vascularity after DSM-embolization. In fact, due to the excessive variability of the arterial vascularization of tumour-bearing livers, hepatic arterial embolization with standard doses of DSMs would induce highly variable effects in terms of arterial flow reduction and redistribution.

Previous studies[34] have indicated that 300–3000 mg of DSMs may have to be used to obtain complete blockage of arterial flow to the liver, as controlled by standard angiography. On the one hand, a low rate of flow reduction and redistribution may nullify the purposes of DSM-embolization, especially with regard to DSM-induced changes in perfusion and flow-related drug uptake of hypovascular masses. This can apply to those cases with hypovascular masses in which a redistribution of flow has not been shown. On the other hand, if more than the optimum amount of DSMs is given, an overflow of microspheres and drug to other organs such as the stomach and duodenum could result in severe pain and vomiting and, possibly, acute mucosal lesions. Furthermore, significant arterial–systemic shunts[35] have been described in several cases with liver tumours studied by hepatic arterial MAA perfusion scanning. After standard dosage DSM-embolization, the rise of the arterial back pressure may cause an increase of arterial pulmonary shunting which can become clinically significant even in previously non-shunting patients.

These considerations appear to be important in chemoembolization with DSMs. An ideal treatment situation is reached when the cytostatic drug is optimally retained in the whole tumour capillary bed without provoking any significant local and systemic toxicity. Consequently, there is a need to individualize DSM-dosages to obtain standard responses in terms of homogeneous distribution of flow to the tumours. For this purpose, a monitoring apparatus has been developed[34] to measure the effects of small pushes of DSMs which are injected serially into the hepatic artery until the expected effects are reached. The degree of capillary blockage is measured by the analysis of the passage through the liver of a radiolabelled low molecular weight substance devoid of hepatic metabolism (^{99m}Tc-methylene diphosphonate). It can be given arterially, mixed with DSMs and traced through the liver to the systemic circulation. The degree of arterial–systemic shunting can be monitored by measuring the systemic passage of ^{99m}Tc-macroaggregated albumin that, under normal conditions, should be almost completely stopped by the hepatic capillary bed.

Finally, the short-lasting effect of the microspheres can be fully exploited only with bolus infusions of drugs. In this setting, the drugs chosen appear to be the alkylating agents, such as mitomycin C which is known to be preferentially toxic to cells under the hypoxic conditions[36] occurring after DSM-embolization. Fluoropyrimidines, which are best given by continuous intra-arterial infusion, seem relatively unsuitable for DSM-chemoembolization. Fluoropyrimidines, however, have a definite role in regional intra-arterial treatment of colorectal liver metastases as they are the most active single agents in gastrointestinal tumours. Indeed, response rates of 55–83 per cent have been reported with combination hepatic arterial chemotherapy including mitomycin C bolus injection associated with continuous infusion of fluoropyrimidines[37,38]. On these bases, a phase I/II clinical trial has recently been activated for the regional treatment of colorectal liver metastases including regional infusion of mitomycin C + 5-FU at the dosages reported above. The total dose of intra-arterial mitomycin C is given as sequential boluses mixed with the required amounts of DSMs as defined according to the above-mentioned monitoring procedure.

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Delayed recovery of hand grip strength predicts postoperative morbidity following major vascular surgery

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Forearm muscle dynamometry was performed in the non-dominant arm in 61 patients undergoing major abdominal and limb vascular surgery, before operation and then 1, 3, 5, and 7 days after surgery. Six patients died in the postoperative period and seven patients developed major postoperative complications (bronchopneumonia, two; wound infection, four; myocardial infarction, one). The preoperative grip strength, measured in kilograms, of the patients who died after major vascular surgery was not significantly lower than that of patients who had an uncomplicated postoperative course. Of the 55 surviving patients, seven developed complications after surgery. These patients had significantly reduced grip strength, expressed as a percentage of the individual preoperative value (P < 0·05), from the first to the seventh postoperative day when compared with patients without complications. The delayed recovery of grip strength preceded the clinical manifestation of complications. These data suggest that delayed recovery of voluntary muscle performance may be used to detect patients developing postoperative complications and so allow their early treatment.

Keywords: Hand grip strength, postoperative complications

Major reconstructive vascular surgery carries appreciable risks of morbidity and mortality[1] owing to factors such as age of the patient and pre-existing medical problems such as myocardial ischaemia, chronic obstructive airways disease and diabetes mellitus[2]. Assessment of voluntary muscle performance by hand grip dynamometry has been used before major abdominal surgery to predict patients at risk of serious postoperative complications[3], but information about recovery of voluntary muscle performance after surgery and its relationship to postoperative complications is lacking. The aims of this study were to record hand grip strength before and after elective vascular surgery and relate this to the development of postoperative complications.

Patients and methods

Sixty-one patients (46 men and 15 women) of median age 66 years (range 41–82 years) who underwent major vascular surgical procedures were studied prospectively. The surgical procedures are shown in *Table 1* None of the patients studied suffered from active gastrointestinal or liver disease which would cause malnutrition and no patient had lost more than 10 per cent of his or her normal body weight in the 6-month period before elective vascular surgery.

Maximal voluntary hand grip strength was measured in the non-dominant arm, using a strain gauge dynamometer[4,5], in all patients before operation and again on postoperative days 1, 3, 5 and 7. Patients with diseases known to affect grip strength, such as rheumatoid arthritis and stroke, were excluded from the study. Grip strength is presented as an absolute value in kilograms for the preoperative evaluation and is matched with one of three possible outcomes, namely no complications after surgery, complications or death. Grip strength is also expressed as a percentage of the preoperative value, thus using each patient as his or her own control, for evaluation after surgery. Statistical analysis is by Student's *t* test.

Patients were reviewed daily and the definitions of postoperative complications were as follows: chest infection required a fever and chest X-ray changes; wound infection required frank discharge of pus from the wound; myocardial infarction required electrocardiographic and myocardial enzyme changes. These complications were classified as major if the patient needed to stay in hospital for more than 14 days after surgery.

Results

Six patients (four men and two women) died within 48 h of surgery, four from myocardial infarction, one from respiratory failure and one from acute renal failure. Seven patients (four men and three women) suffered major postoperative complications requiring prolonged hospitalization, comprising four wound infections, two bronchopneumonias and one myocardial infarction.

Preoperative assessment of hand grip strength, in kilograms, related to outcome is shown in *Table 2*. There was a trend towards reduced grip strength in both the men and women who died or suffered postoperative complications, when compared with patients with an uncomplicated postoperative course, but this trend was not statistically significant.

Table 1 *Surgical procedures in 61 patients*

Surgical procedures	*n*
Graft for aortic aneurysm	22
Aortobifemoral graft	14
Femorofemoral graft	6
Femoropopliteal graft	17
Lumbar sympathectomy	1
Femoral endarterectomy	1
Total	61

Table 2 *Mean preoperative hand grip strength matched with outcome*

Outcome	No. of men	Grip strength (kg)	No of women	Grip strength (kg)
No complications	38	30·2 (8·4)	10	14·9 (5·7)
Complications	4	25·4 (9·1)	3	14·4 (4·3)
Death	4	27·4 (5·8)	2	13·0 (4·2)

Values in parentheses are standard deviations

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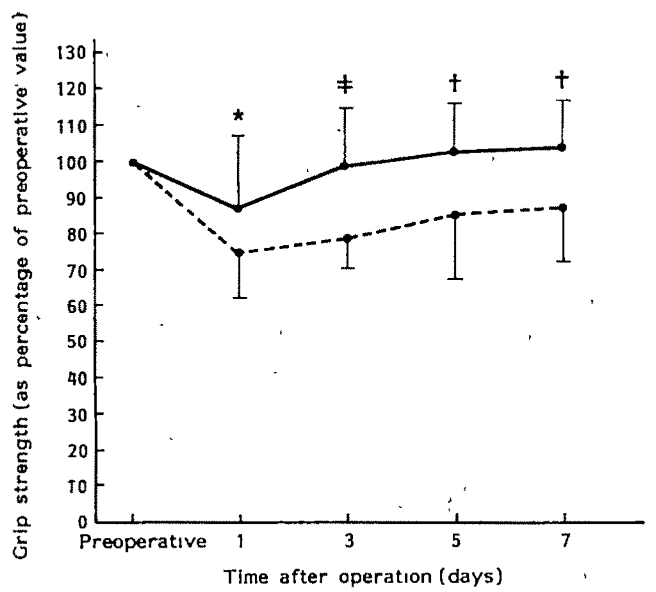

Figure 1 *Grip strength after surgery, expressed as a percentage of preoperative value, in patients with* (– – –) *postoperative complications* (n=7) *and in patients without* (——) *postoperative complications* (n=48) *the points are means with standard deviation bars.* *, $P<0\cdot05$, †, $P<0\cdot01$, ‡, $P<0\cdot0001$

All patients showed a depression of hand grip strength, expressed as a percentage of the preoperative value, after major vascular surgery. In patients who had an uncomplicated postoperative recovery, grip strength returned to preoperative levels by the third postoperative day (*Figure 1*). In the seven patients who developed major postoperative complications, grip strength was significantly lower on the first postoperative day compared with that of the patients with an uncomplicated recovery ($P<0\cdot05$) and became very significantly depressed by the third postoperative day when compared with the grip strength of the no complication group ($P<0\cdot001$). Hand grip strength remained depressed in the group with complications until the end of the study on the seventh postoperative day. The phenomenon of reduced grip strength in the patients who subsequently developed major postoperative complications was noted up to several days before the complication was clinically apparent by the previously defined criteria.

Discussion

Previous studies of voluntary muscle performance using hand grip dynamometry[3,6] have shown that reduced expected grip strength for a patient's age and sex can predict those who are at major risk of dying or developing serious postoperative complications after major abdominal surgery. Grip strength recovers rapidly after minor surgery, such as hernia repair, and operations of more stressful nature, such as cholecystectomy. This rapid recovery of hand grip strength does not correlate with the condition of postoperative fatigue which may last for months after surgery[7,8]. In our study, all patients had reduced grip strengths on the first postoperative day, but by the third day hand grip strength had returned to normal in those patients who had an uncomplicated recovery. The findings that postoperative grip strength is reduced in patients who will subsequently develop complications has not previously been reported. This phenomenon may well be of predictive value in alerting the surgeon to a patient who is at high risk of developing a major postoperative complication, enabling early appropriate treatment, for example physiotherapy and antibiotics for chest infection.

The failure of hand grip strength when taken as a single preoperative measurement effectively to predict those vascular surgical patients who subsequently die or develop postoperative complications is disappointing, as it appears to be effective in patients undergoing major abdominal surgery[3,6]. It may be that grip strength is a poor indicator of myocardial ischaemia which was the major cause of postoperative death in four out of the six patients who died in the present series. Grip strength is more effective in identifying patients at risk of septic complications[6] after surgery and is known to be reduced in patients with acute infectious diseases[9]. Why grip strength should be reduced in patients with septic complications is unknown but it may be due to impaired function of the forearm muscles responsible for grip strength. Muscle biopsies in patients with infectious diseases show reduced activity of sarcoplasmic enzymes[10,11], which may reduce the availability of energy-rich phosphates causing muscle weakness. Alternatively, apparent muscle weakness may be due to a central effect[11] as a result of disturbance of the pathway from the cerebral motor cortex to the forearm muscles.

Further research in this area should identify the level of impairment of voluntary muscle performance in patients with septic complications. For the present, the observation that the delay in return of hand grip strength to preoperative values occurs up to 48 h in advance of the developing complication is of interest, as it may allow early treatment for expected postoperative complications.

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Ultrasound guided percutaneous pancreatic biopsy

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A major obstacle to the diagnosis and understanding of pancreatic exocrine disease has been the inability to obtain histological samples safely without resort to laparotomy. Surgeons are reluctant to biopsy the pancreas in view of the recognized frequency of complications, especially using large calibre needles[1–3]. The disadvantage of fine needle aspiration biopsy for pancreatic diagnosis is that only a cytological sample is obtained.

We report our initial experience with a recently developed system of percutaneous, targeted organ biopsy under ultrasound guidance that provides a histological sample[4] which we have applied to pancreatic biopsy.

Patients and methods

Biopsies were performed on fasting, consenting patients with a normal coagulation screen. An 18 gauge Tru-cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) biopsy needle was mounted in an automatic firing device employing a spring-loaded mechanism[4] (Biopty®, Radiplast AB, Uppsala, Sweden) that is operated with one hand, enabling simultaneous ultrasound scanning. The needle tip and biopsy track can be seen ultrasonically to confirm precise targeting. An initial scan is performed to plan the biopsy route avoiding the liver and major vessels as well as, if possible, the colon, although most biopsies were performed transgastrically Using an aseptic technique and local anaesthesia the needle was advanced under ultrasound guidance to the edge of the pancreas or mass lesion

Thirty-eight patients were prepared for biopsy, which was not attempted in five patients because hepatomegaly obscured the pancreas. Pancreatic biopsy was attempted in 33 patients (19 men and 14 women) aged 36–74 years (*Table 1*). The most common indication was a pancreatic mass lesion found at ultrasound in 23 patients, of whom 11 were jaundiced; 17 were considered clinically to have pancreatic carcinoma and the other six to have chronic pancreatitis. Three patients with pancreatitis had a biopsy because an unusual cystic lesion was detected. Seven patients with recurrent abdominal pain and equivocal investigations were suspected of having chronic pancreatitis.

Results

The only complication was severe abdominal pain in two patients which resolved spontaneously. Biopsy failed in two patients. Sample size varied from 13 × 2 mm to 4 × 3 mm.

The results are shown in *Table 1*. Pancreatic biopsy provided the correct diagnosis in all cases. Neoplasms were confirmed at laparotomy or autopsy. Chronic pancreatitis was diagnosed on the basis of calcification (three), abnormal pancreatograms (nine), exocrine dysfunction (five) or laparotomy (two) and all have been followed clinically for over 1 year. Whilst biopsy merely confirmed the clinical and ultrasound diagnosis in 21 of 33 patients it excluded neoplasia in four of six patients with chronic pancreatitis and an ultrasound mass. It diagnosed the non-pancreatic origin of three tumours and one unsuspected islet cell tumour and provided a diagnosis in six of seven patients with equivocal investigations. It should be noted that in four of 12 non-jaundiced patients (33 per cent) with a pancreatic mass at ultrasound, the clinical diagnosis was erroneous.

Discussion

In 1982, Lindgren[4] described a percutaneous needle biopsy technique for kidney and liver with several practical advantages. Simultaneous ultrasound scanning confirms correct biopsy targeting and a histological sample is provided. Satisfactory specimens were obtained in all cases, with one minor bleeding episode[4]. There are no published results of this technique for pancreatic biopsy, although it is mentioned in a recent review[5] that the authors' experience with 40 patients indicated a higher accuracy than with fine needle aspiration biopsy.

The results of this study suggest that it is a reliable technique. All tumours have been confirmed subsequently and patients with pancreatitis show no evidence of neoplasia on follow-up. Estimates of sensitivity and specificity are inappropriate. We have infrequently encountered the well recognized difficulty in histological distinction between carcinoma and chronic pancreatitis, perhaps because of the biopsy size. The availability of a histological diagnosis had a major impact on clinical management.

Table 1 *Indications for biopsy and results*

Indication for biopsy (number)	Initial clinical diagnosis	Number of patients	Final histological diagnosis	Number of patients
Ultrasound, mass + jaundice (11)	Pancreatic carcinoma	10	Pancreatic carcinoma	10
	Chronic pancreatitis	1	Chronic pancreatitis	1
Ultrasound, mass alone (12)	Pancreatic carcinoma	7	Pancreatic carcinoma	4
			Ampulla carcinoma	1
			Gastric carcinoma	1
			Lymphoma	1
	Chronic pancreatitis	5*	Chronic pancreatitis	3
			Insulinoma	1
Equivocal investigations (7)	Pancreas divisum	3*	Chronic pancreatitis	1
			Normal	1
	Uncertain	4	Chronic pancreatitis	3
			Normal	1
Ultrasound, cyst (3)	Chronic pancreatitis	1	Chronic pancreatitis	1
	Acute pancreatitis	2	Acute pancreatitis	2

* Biopsy failed in one patient of each group

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The crucial question, however, is whether this procedure is safe. The risk of biopsy increases with the needle size employed; thus, biopsy with a 22 gauge needle carries a mortality rate of 1:20 000 and a complication rate of under 1 per cent[5,6] and, conversely, biopsy with 14 gauge needles has a mortality rate of up to 9 per cent and a complication rate of 7·5–14 per cent[1-3]. One would predict an intermediate complication rate for this technique, which should not be undertaken without a good clinical indication until its safety is established. There are few disadvantages to this biopsy technique; the equipment is inexpensive and most hospitals possess real-time ultrasound equipment and facilities for histological assessment. The main problem has been the presence of hepatomegaly obscuring the pancreas, but transgastric (usually) and transcolonic (occasionally) biopsies have not caused problems.

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Relationship between bile acid malabsorption using the ^{75}Se homocholic acid taurine scanning method and diarrhoea following right hemicolectomy

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Diarrhoea following right hemicolectomy occurs in up to 50 per cent of patients[1]. Malabsorption of bile acids due to resection of the terminal ileum is thought to be important in the pathogenesis of these postoperative symptoms[2], hence changes in the bile acid pool have been investigated following right hemicolectomy using selenium-75 homocholic acid taurine (^{75}SeHCAT, Amersham International plc, Amersham, UK) scanning in order to define the relationship between bile acid malabsorption and symptomatic diarrhoea.

Patients and methods

To evaluate the temporal relationship between bile acid malabsorption and diarrhoea the bile acid pool was examined in 21 patients undergoing right hemicolectomy, using 7-day ^{75}SeHCAT scanning (*Table 1*) Seven patients had Crohn's disease of the terminal ileum and 14 had carcinoma of the caecum The length of unstretched small bowel resected was recorded before fixation.

A previously described method of ^{75}SeHCAT scanning was used with minor modifications[3] ^{75}SeHCAT 37×10^4 Bq was administered orally after an overnight fast. ^{75}Se activity was measured using a large field γ camera (Elscint Dymax LF, Israel) interfaced with an Elscint Dycom 80 computer. After an equilibration period of 4 h, the gallbladder area was counted with the patient supine and prone for 5 min each The procedure was repeated after 7 days and retention was expressed as a percentage ratio of the counts on day 7 to the counts on day 0

^{75}SeHCAT scanning was not possible in all cases because of partial or complete intestinal obstruction. Eleven patients were studied preoperatively, 21 patients at between 2 and 11 weeks after surgery and 18 patients at 44–80 weeks. In patients with Crohn's disease there was no clinical evidence of active disease during the study period Ten patients were treated postoperatively with antidiarrhoeal agents (*Table 1*)

Table 1 *Details of all patients included in the ^{75}SeHCAT study*

No.	Sex	Age (years)	Diagnosis	Length of ileum resected (cm)	*Diarrhoea Early	*Diarrhoea Late	Treatment
1	Female	66	Crohn's disease	47	+	–	Loperamide
2	Female	74	Carcinoma of the caecum	10	+	–	Cholestyramine
3	Male	48	Crohn's disease	38	+	–	Loperamide
4	Male	82	Carcinoma of the caecum	6	+	–	Diphenoxylate
5	Female	23	Crohn's disease	67	–	–	–
6	Male	69	Carcinoma of the caecum	10	–	†	–
7	Male	49	Carcinoma of the caecum	21	–	–	–
8	Female	74	Carcinoma of the caecum	14	+	–	Loperamide
9	Male	47	Crohn's disease	23	–	–	–
10	Female	71	Carcinoma of the caecum	36	+	–	Diphenoxylate
11	Female	80	Carcinoma of the caecum	18	+	+	Cholestyramine
12	Female	54	Carcinoma of the caecum	34	–	–	–
13	Male	76	Carcinoma of the caecum	62	–	†	–
14	Female	53	Carcinoma of the caecum	17	–	†	–
15	Male	66	Carcinoma of the caecum	32	–	–	–
16	Female	66	Crohn's disease	81	+	+	Cholestyramine
17	Female	48	Carcinoma of the caecum	30	+	+	Diphenoxylate
18	Male	75	Carcinoma of the caecum	4	+	–	Loperamide
19	Male	22	Crohn's disease	48	–	–	–
20	Female	64	Carcinoma of the caecum	15	–	–	–
21	Female	56	Crohn's disease	27	–	–	–

*Symptoms reported while off any antidiarrhoeal therapy; † patient died before final study. ^{75}SeHCAT, selenium-75 homocholic acid taurine

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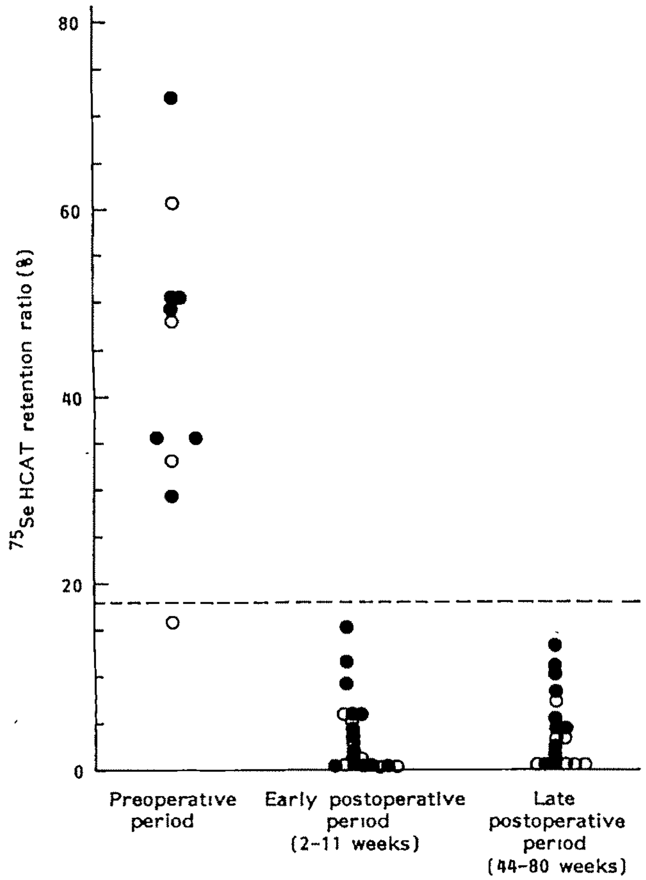

Figure 1 *Seven-day selenium-75 homocholic acid taurine (^{75}SeHCAT) retention ratios in the preoperative and postoperative periods (values <19 per cent indicate bile acid malabsorption, Reference 4).* ○, *Crohn's disease;* ●, *caecal cancer*

Medication was discontinued at least 1 week before scanning. Daily records of stool frequency and consistency were kept by each subject, while not taking medication, in the early and late postoperative periods. Diarrhoea was defined as three or more loose or poorly formed motions per day, while off treatment

Statistical analyses were performed using the Mann–Whitney *U* test and the Spearman rank correlation. Significance was defined as $P < 0.05$. The study was approved by the District Ethical Committee.

Results

The median preoperative ^{75}SeHCAT retention ratio was 44·3 per cent (range 17–73 per cent; normal value >19 per cent) compared with the significantly lower early postoperative value of 3·5 per cent (range 0–15 per cent, $P < 0.001$) and the late postoperative value of 3·0 per cent (range 0–14·5 per cent, $P < 0.001$; *Figure 1*).

The median length of small bowel resected was 27 cm (range 4–81 cm; *Table 1*). There was no significant correlation between the length of small bowel resected and the ^{75}SeHCAT retention (early postoperative period $r = 0.13$, $P = 0.59$; late postoperative period $r = 0.05$, $P = 0.84$).

In the early postoperative period ten of the 21 subjects (48 per cent) had diarrhoea (median stool frequency 4 per day, range 0·5–10 per day) compared with only three of 18 (17 per cent) in the late postoperative period (2 per day, range 0·33–6 per day, $P = 0.013$). Adequate control of symptoms was achieved using standard medication in seven of the ten patients in the early postoperative phase and in two of the three patients in the late postoperative period.

There was no significant correlation between the length of ileum resected and postoperative stool frequency, in either the early ($r = 0.17$, $P = 0.46$) or late postoperative periods ($r = -0.21$, $P = 0.41$). There was also no correlation between the degree of postoperative diarrhoea and ^{75}SeHCAT values (early $r = 0.13$, late $r = 0.05$).

Discussion

Results of ^{75}SeHCAT studies are comparable to faecal [^{14}C]taurocholate determination, but without the disadvantages of the latter technique[4] In our study, malabsorption of bile acids following right hemicolectomy was universal and supports earlier published data from a study of bile acid malabsorption following ileal resection[5]. In contradiction to earlier studies no correlation was found between the length of ileum resected and the degree of bile acid malabsorption[6]. Patients with ileal resections and intact ileocaecal valves have previously been noted to absorb bile acids better and have less diarrhoea than those in whom the valve had been removed[1]. This suggests that bile malabsorption could be exacerbated by rapid intestinal transit.

Although there was no improvement in bile acid reabsorption during follow-up, significant reduction in stool frequency occurred in seven of ten patients. Both small and large bowel adaptation may be responsible for this effect. The symptomatic improvement seen in the late postoperative period may also be the result of the return of normal intestinal flora in the colon. Anaerobic bacteria are important in generating short-chain fatty acids from dietary fibre and these can counteract the inhibitory effects of bile acids on colonic sodium and water reabsorption[7,8].

In benign disease preservation of the ileocaecal valve and the right colon seems desirable. Further studies are required to clarify the adaptive processes which appear to occur following right hemicolectomy.

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Human fasting and postprandial sphincter of Oddi motility

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Sphincter of Oddi motility was evaluated in post-cholecystectomy patients with indwelling T tubes during fasting and after feeding. A triple-lumen catheter was positioned to record from the sphincter of Oddi and duodenum. The sphincter of Oddi was characterized by phasic contractions independent of duodenal contractions. During fasting duodenal wave frequency exhibited four phases, whereas only two phases could be identified from the sphincter of Oddi. A prolonged phase A in the sphincter of Oddi corresponded to duodenal phases I, II and IV. A short phase B in the sphincter of Oddi just preceded the onset of duodenal phase III and was temporally related to it. Sphincter of Oddi basal pressure increased during duodenal phases III and IV. After ingestion of food, sphincter of Oddi basal pressure, wave amplitude and duration decreased, but the frequency remained unchanged. Conversely, duodenal frequency increased but there was no change in amplitude. Thus, the human sphincter of Oddi and duodenum exhibited independent motility demonstrating distinct phases during the interdigestive period. After food, sphincter of Oddi motility altered in a manner which would facilitate the passive flow of fluid into the duodenum.

Keywords: Manometry, biliary tract, duodenum, sphincter of Oddi

The sphincter of Oddi has a major role in the control of bile flow and flow of pancreatic juice. Studies in man and animals have shown that the sphincter of Oddi is characterized by phasic contractions which are superimposed on a modest tone[1,2]. In animals, the phasic contractions have been shown to obstruct flow transiently[3], but their main effect is to propel small volumes of fluid from the bile duct into the duodenum[4–6]. In addition, cineradiography has demonstrated some passive flow of fluid occurring between the phasic contractions[6]. Studies in man suggest a similar mechanism to that described in animals; however, the balance between active propulsion across the sphincter of Oddi *versus* passive flow remains uncertain[7–9].

In this study we have examined the motility of the sphincter of Oddi in patients who have recovered from bile duct exploration for stones and who have a T tube in the bile duct. The presence of a T tube in the bile duct permitted prolonged manometric studies to assess the interdigestive pattern of the human sphincter of Oddi and its response to the ingestion of a meal.

Patients and methods

Thirteen patients undergoing cholecystectomy and common duct exploration for stones were studied. All patients had both gallbladder and common bile duct stones and none had experienced pancreatitis in the past. There were seven men and six women with a median age of 60 years (range 40–80 years). Studies were attempted in a further six patients but failed for technical reasons. One patient experienced pain when the tip of the catheter entered the sphincteric region and in the other five the sphincter of Oddi could not be cannulated. The study was approved by the Clinical Investigations Committee of Flinders Medical Centre in May 1985, with informed written consent for inclusion in the study being obtained from all patients.

Operative procedure

Cholecystectomy was performed and bile duct exploration carried out via a longitudinal supraduodenal choledochotomy. The sphincter of Oddi was not manipulated by rigid instruments and all stones were removed. A modified latex rubber T tube was positioned in the bile duct and the duct was closed with a fine absorbable suture. The T tube was modified (*Figure 1*) by passing a 25-cm long 8 or 10 Fr soft polyvinyl chloride catheter (Nelaton®, Australian Hospital Supplies, Sydney, Australia) through the long arm and positioning its tip such that it would direct the manometry catheter towards the sphincter of Oddi. The polyvinyl chloride catheter was secured within the long external arm of the latex rubber tube with two circumferential silk sutures.

A tube choledochogram was obtained 1 week postoperatively and, if no abnormality was detected, the external limb of the T tube was occluded. The patient was discharged from hospital with the T tube *in situ*, as has been our custom, and allowed to return to a normal diet. Sphincter of Oddi manometric studies were done 1–2 weeks after closure of the T tube, thus allowing for the re-establishment of normal enterohepatic circulation of bile salts[10] and for a firm tract to form around the tube, reducing the chance of bile fistula on removal.

Sphincter of Oddi manometry was performed after a 12-h overnight fast. Medications likely to affect gastrointestinal motility were stopped on the day before study and all extraneous gustatory stimuli were eliminated.

T tube manometry

Pressure recordings from the bile duct, sphincter of Oddi and the duodenum were accomplished using a polyethylene triple lumen side

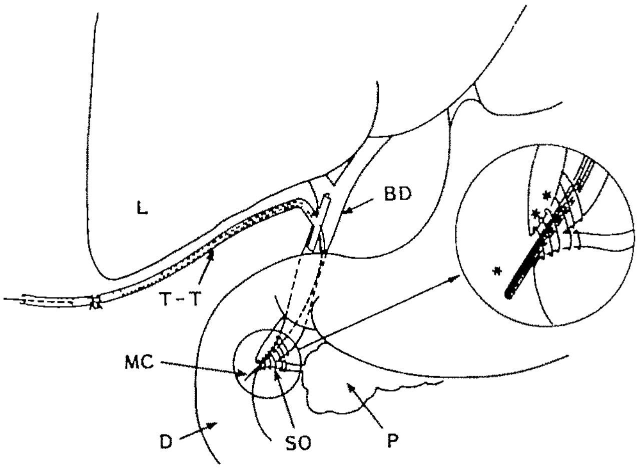

Figure 1 *Schematic representation of the sphincter of Oddi (SO), duodenum (D), bile duct (BD), liver (L) and pancreas (P) with the modified T tube (T-T) and triple lumen manometry catheter (MC) in situ. The inset shows the position of the recording holes (*) within the sphincter of Oddi segment and duodenum*

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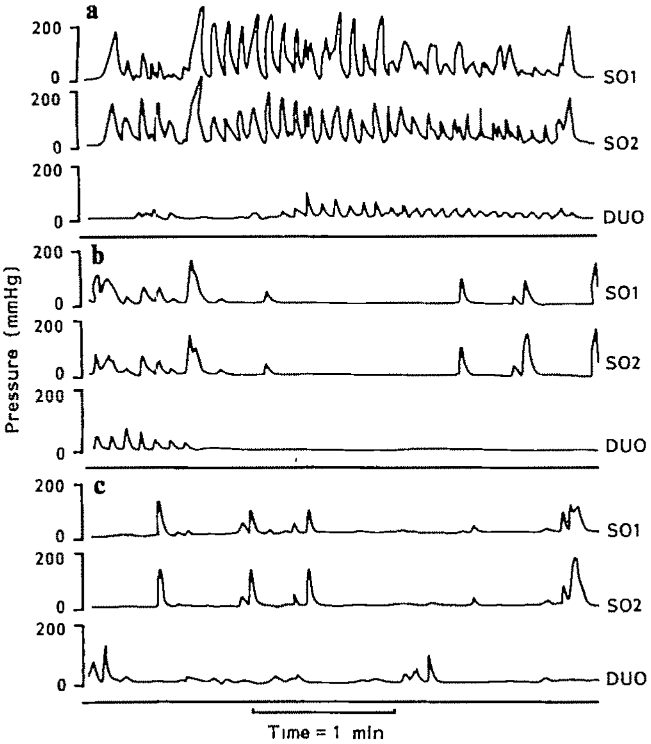

Figure 2 *Manometric recordings from the proximal (SO1) and distal (SO2) sphincter of Oddi and duodenum (DUO).* **a** *Demonstration of an activity front: its onset in the sphincter of Oddi precedes its duodenal onset.* **b** *End of activity front. the sphincter of Oddi contracts during duodenal phase I.* **c** *Duodenal phase II the sphincter of Oddi and duodenum contract independently*

hole manometric catheter, having an outer diameter of 1·0 mm, luminal diameters of 0·35 mm and a length of 1·0 m (Dural Plastics and Engineering, Auburn, Australia). The three side holes were respectively 5, 20 and 22 mm from the end of the catheter. The catheter was marked every 1 cm from the proximal side hole.

During pressure recording, each catheter lumen was infused with sterile, bubble-free water at a rate of 0·25 ml/min by a minimally compliant hydraulic capillary infusion system[11], using a reservoir pressure of 400 mmHg. Abrupt obstruction of the recording orifice of each recording lumen generated a pressure rise rate in excess of 350 mmHg/s. Each recording channel was connected via a pressure transducer to a polygraph run at a chart speed of 10 cm/min.

Recording was performed with the patient supine in bed. The external limb of the T tube was opened and the T tube and surrounding skin were disinfected with antiseptic solution. The sterilized triple lumen catheter was passed through the modified T tube into the bile duct and advanced through the sphincter of Oddi so that all three recording lumens were positioned in the duodenum. The recorded pressures were then adjusted so that duodenal basal pressure acted as the zero reference.

The manometry catheter was then withdrawn in a stepwise fashion so that the two proximal side holes were positioned within the sphincter of Oddi and the distal side hole remained in the duodenum The correct position of the recording catheter in the sphincter of Oddi was determined by the demonstration of a high pressure zone on the withdrawal of the manometry catheter from the duodenum into the sphincter of Oddi The correct catheter position was then confirmed by relating the distance the catheter was passed to the length of the T tube and the distance from the T tube to the sphincter of Oddi, as calculated from the choledochogram.

During the recording session the external arm of the T tube was left open, avoiding any increase in bile duct pressure which may have been produced by perfusion into the biliary system A small volume of bile leaked out of the open arm of the T tube and around the manometry catheter.

Preliminary recordings progressed until the first duodenal activity front was observed. This was characterized by an increase in the frequency and amplitude of duodenal contractions, followed by a period of quiescence (*Figure 2a* and *b*)[12]. If the first activity front occurred within 2 h of the start of recording and the patient was tolerating the procedure, recording continued until a second activity front was observed, thus recording a complete interdigestive cycle.

Thirty minutes after an activity front a cephalic gustatory stimulus was given: this consisted of the sight and smell of a hot aromatic meal of meat and vegetables for 1 min, followed by talk of food for a further 9 min A composite liquid test meal, consisting of 375 ml of Sustain® (Mead Johnson, Crows Nest, Australia; 13·5 g fat, 24·3 g protein, 52·5 g carbohydrate: 1750 kJ), was then ingested over 5 min Recording continued for a further 35 min or as tolerated. The total recording session lasted up to 5 h

Scoring of the manometric tracings were carried out manually and independently by two observers. Sphincter of Oddi basal pressure was referenced to duodenal pressure taken as zero and the lowest sustained sphincter of Oddi pressure for each interval was used. The amplitude of the sphincter of Oddi phasic contractions was calculated by subtracting the basal sphincter of Oddi pressure from the peak pressure. Pressure changes of less than 10 mmHg and waves characterized by an acute pressure rise rate of more than 300 mmHg/s were excluded from analysis as they represented artefacts[13]. Less than 5 per cent of total waves were excluded using these criteria. The sphincter of Oddi wave frequency was expressed as contractions per minute. Wave duration was calculated by measuring the time in seconds between the upstroke and downstroke of each contraction. Sequencing of sphincter of Oddi contractions was not determined for this study as the distance between the two lumens positioned in the sphincter would not allow accurate assessment. For analysis of the interdigestive cycle, the period between two activity fronts was normalized by division into 2 per cent intervals. The mean of the sphincter of Oddi basal pressure, wave amplitude, frequency and wave duration, were calculated for each 2 per cent interval as well as the duodenal wave amplitude and frequency. Duodenal phasic activity was analysed by adaptation of the criteria of Code and Marlett[14]. Phase I was characterized by a relative absence of phasic contractions compared with other phases. The onset of phase II occurred when the frequency of contraction was constantly greater than 1/min. Phase III started when the duodenum was contracting at the maximal observed rate Phase IV was the transitional period between phase III and the subsequent phase I.

The response to food was analysed by taking a control period of 10 min before food presentation and comparing it with the 10 min of cephalic gustatory stimuli, the 5-min ingestion period and the subsequent six consecutive 5-min intervals after ingestion For each period the mean sphincter of Oddi basal pressure, wave amplitude, duration and frequency were determined. In addition, a separate comparison was made between the mean of a 10-min preingestion period and the mean of the 20-min period immediately after ingestion.

Statistical analysis

Statistical analysis was performed using Minitab® (Minitab Data Analysis Software, University Park, Pennsylvania, USA) interfaced to a Prime mainframe computer (Prime Computer Corporation, Natick, Massachusetts, USA). Normality of distribution of the data was assessed using the Shapiro–Wilk test[15]. For normally distributed data, a paired *t* test was used and non-parametric analyses were performed using the Sign test (significance, $P < 0·05$). Data are presented in the text as mean (s.d.) unless otherwise stated

Results

In the 13 patients, a total of 19 activity fronts (*Figure 2a*) were recorded, two consecutive fronts being recorded in six patients, thus allowing normalization of six complete interdigestive cycles. Because of catheter displacement during the activity front, complete recording from the duodenum and sphincter of Oddi was not possible in three of 19 and one of 19 patients respectively, resulting in 16 duodenal and 18 sphincter of Oddi activity fronts for analysis.

Interdigestive activity of the duodenum (Figure 3)

The duodenal interdigestive cycle could be divided into four phases. Phase I consisted of a relatively quiescent period. Phase II consisted of an irregular contraction period which culminated in phase III (comprising the activity front). Phase III was characterized by a rapid contraction frequency of 11·9 (1·8) contractions/min, a wave duration of 3·9 (2·2) s and wave amplitude of 30 (7) mmHg. Phase IV then followed, during which the frequency of contraction differed significantly from phase I and phase III. The length of the duodenal interdigestive cycle was 100 (33) min.

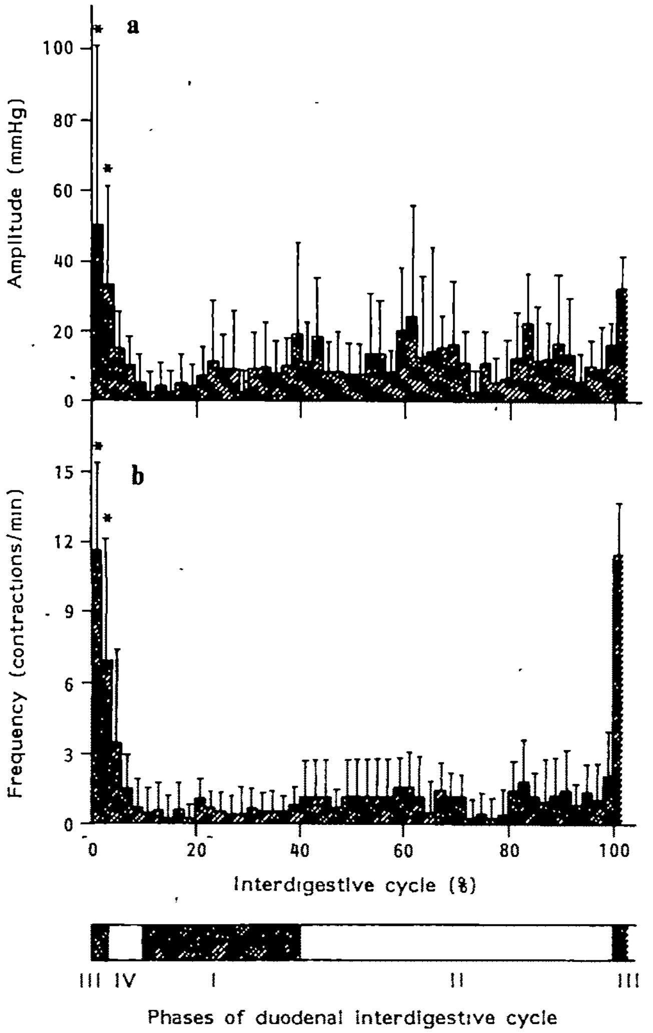

Figure 3 *Histograms of duodenal wave* **a** *amplitude and* **b** *frequency over 100 per cent of the interdigestive cycle. The interdigestive cycle is divided into 2 per cent intervals and values are expressed as the mean (s.d.) for six patients. Duodenal activity is separated into four phases and is recorded at the bottom of the figure, *denotes a significant difference compared with phases I and II*

Interdigestive activity of the sphincter of Oddi (Figure 4)

Throughout the interdigestive cycle the sphincter of Oddi demonstrated contractile activity which was visually divided into two phases (A and B).

During phase A, the sphincter of Oddi contracted at a frequency of 3·0 (1·3) min, the wave amplitude was 79 (35) mmHg and the wave duration was 5·0 (1·6) s. The basal pressure was 8 (6) mmHg and the duration of phase A was 96 (32) min.

Phase B (the activity front) consisted of a period of rapid contraction, at a frequency of 10·4 (1·4) min, lasting 4·5 (2·4) min. The wave amplitude was significantly greater during phase B compared with phase A (101 (35) *versus* 79 (35) mmHg). There was a significant increase in basal pressure during phase B (13 (6) *versus* 8 (6) mmHg), which persisted into early phase A. The wave duration did not vary significantly between phases A and B (5·0 (1·6) *versus* 5·5 (1·8) s). The length of the sphincter of Oddi interdigestive cycle was 100 (33) min.

Relationship of sphincter of Oddi to duodenal interdigestive cycle activity

A close relationship existed between the phasic contraction patterns of the sphincter of Oddi and duodenum during the interdigestive cycle (*Figure 2*).

The phasic contractions recorded from the sphincter of Oddi and duodenum were independent of each other. The sphincter of Oddi and duodenal interdigestive cycle lengths were virtually identical; however, the onset of the sphincter of Oddi activity front preceded the duodenal activity front by a median of 6 s (range 2–62 s) on all but three of the 16 occasions when complete sphincter of Oddi and duodenal activity fronts were recorded. In those three, the onsets coincided. The contraction frequency during the sphincter of Oddi activity front was significantly less than that of the duodenal front (10·4 (1·4) *versus* 11·9 (1·9) min), and the wave amplitude was significantly greater (101 (35) *versus* 30 (7) mmHg). The duration of the sphincter of Oddi activity front was significantly greater than the duodenal front (4·5 (2·4) *versus* 3·9 (2·2) min)

Although four phases were identified in the duodenal interdigestive cycle, the sphincter of Oddi only demonstrated two phases. Duodenal phases I and II coincided with sphincter of Oddi phase A, whilst duodenal phase III coincided with

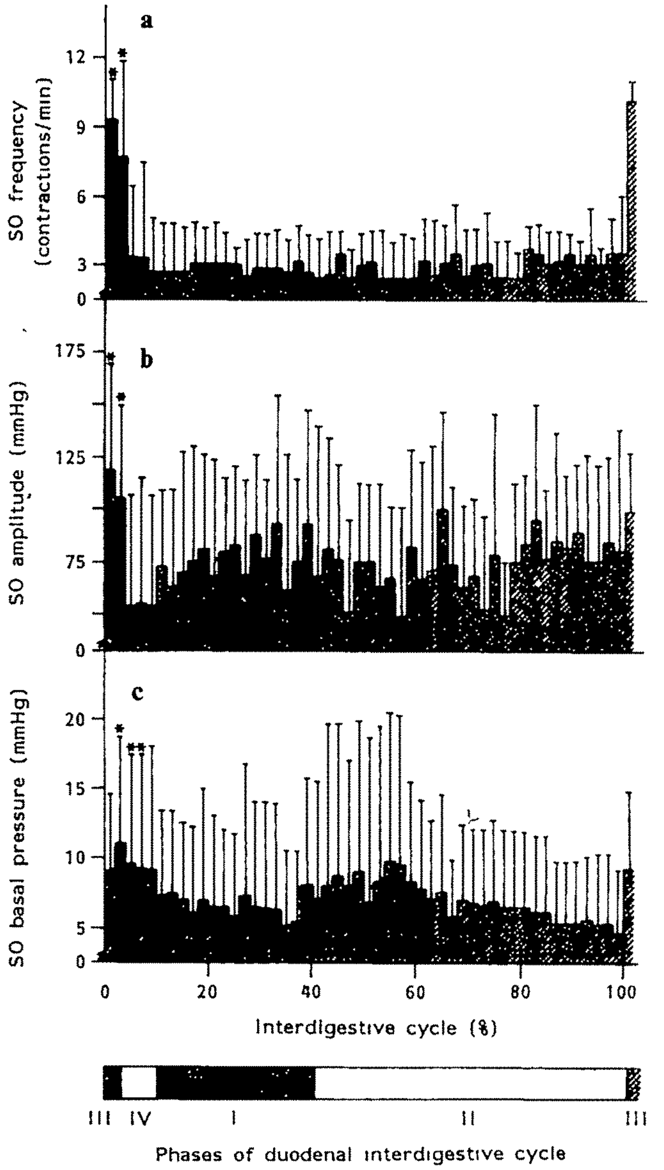

Figure 4 *Histograms of sphincter of Oddi (SO) wave* **a** *frequency* **b** *amplitude and* **c** *basal pressure over 100 per cent of the interdigestive cycle. The interdigestive cycle is divided into 2 per cent intervals and values are expressed as the mean (s d.) for six patients. The four phases of the duodenal interdigestive cycle are recorded at the bottom of the* Figure *Sphincter of Oddi contractions are omnipresent throughout the interdigestive cycle and are visually divided into two phases. The long phase corresponds to duodenal phases I, II and IV A short phase just precedes and is related to duodenal phase III, *denotes a significant difference compared with phases I and II*

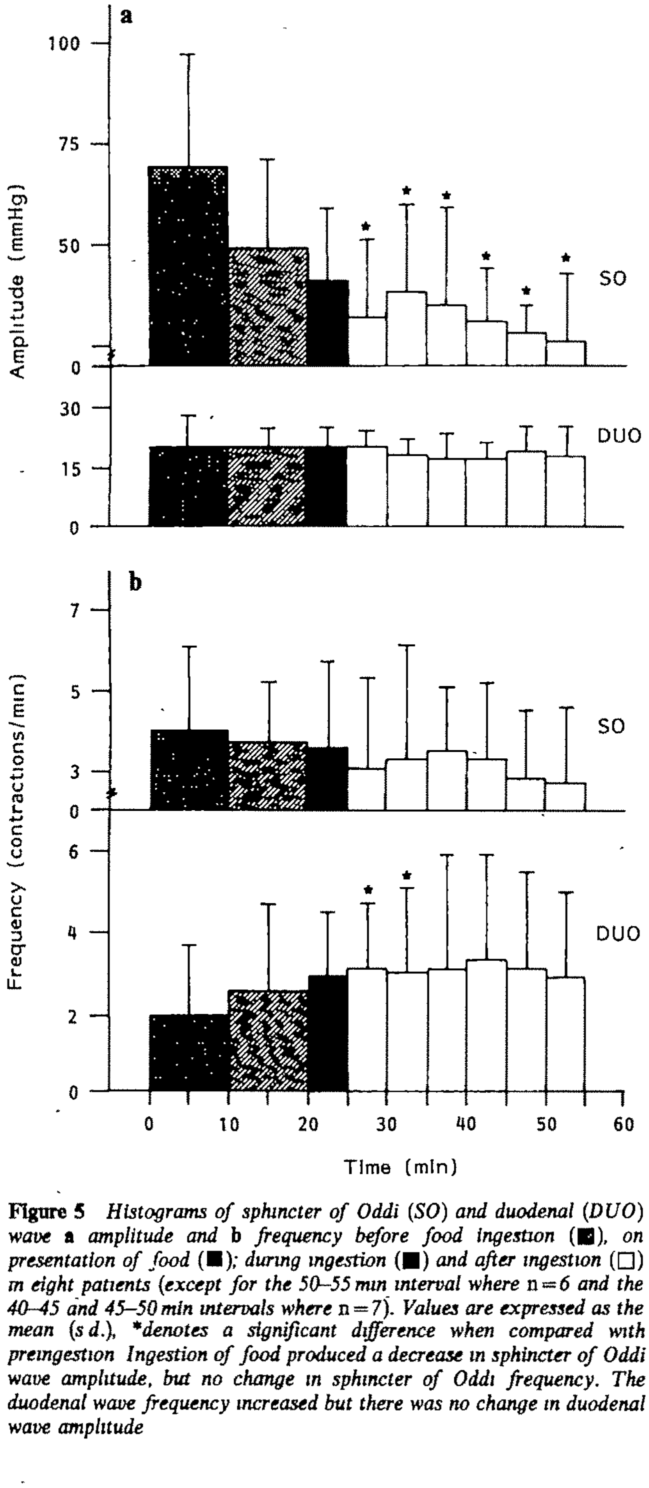

Figure 5 *Histograms of sphincter of Oddi (SO) and duodenal (DUO) wave* **a** *amplitude and* **b** *frequency before food ingestion* (■), *on presentation of food* (■)*; during ingestion* (■) *and after ingestion* (□) *in eight patients (except for the 50–55 min interval where* n = 6 *and the 40–45 and 45–50 min intervals where* n = 7)*. Values are expressed as the mean (s.d.), *denotes a significant difference when compared with preingestion Ingestion of food produced a decrease in sphincter of Oddi wave amplitude, but no change in sphincter of Oddi frequency. The duodenal wave frequency increased but there was no change in duodenal wave amplitude*

sphincter of Oddi phase B. Duodenal phase IV overlapped the junction of sphincter of Oddi phases A and B. The sphincter of Oddi basal pressure demonstrated a significant rise during duodenal phases III and IV.

Effect of feeding on sphincter of Oddi and duodenal activity (Figures 5 *and* 6)

The sight and smell of food did not significantly alter the contractile pattern of the sphincter of Oddi or duodenum, although a trend towards a decrease in sphincter of Oddi wave amplitude was observed.

Feeding produced a significant reduction in the sphincter of Oddi wave amplitude duration and basal pressure. There was no significant effect on sphincter of Oddi wave frequency and specifically the sphincter of Oddi contractions persisted in five of the eight patients. Contractions were abolished for periods of 9, 15 and 18 min respectively in the other three patients. Duodenal wave amplitude did not alter significantly after food but there was a significant increase in frequency.

Effect of modified T tube and manometry on the patients' clinical progress

The modification of the T tube did not alter the management of the patients included in the study. Length of hospital stay was no different to that of patients who were not studied and there were no complications that could be attributed to the modified T tube. The patients tolerated the manometric studies without complication and on completion of the study the T tube was removed. Follow-up of these patients 1 month after the studies revealed no abnormalities that could be attributed to either the modified T tube or the manometric study.

Discussion

In this study we evaluated the motility of the human sphincter of Oddi during the interdigestive period and after a meal. We related the activity of the sphincter of Oddi to that of the duodenum during both the fasting and postprandial periods. The major findings from this study were:

1. The sphincter of Oddi demonstrated phasic contractions which were independent of duodenal contractions
2. In the interdigestive period the sphincter of Oddi contractions showed two distinct phases: a prolonged phase of continuous contractions which corresponded to duodenal phases I, II and IV contractions, and a short phase of rapid

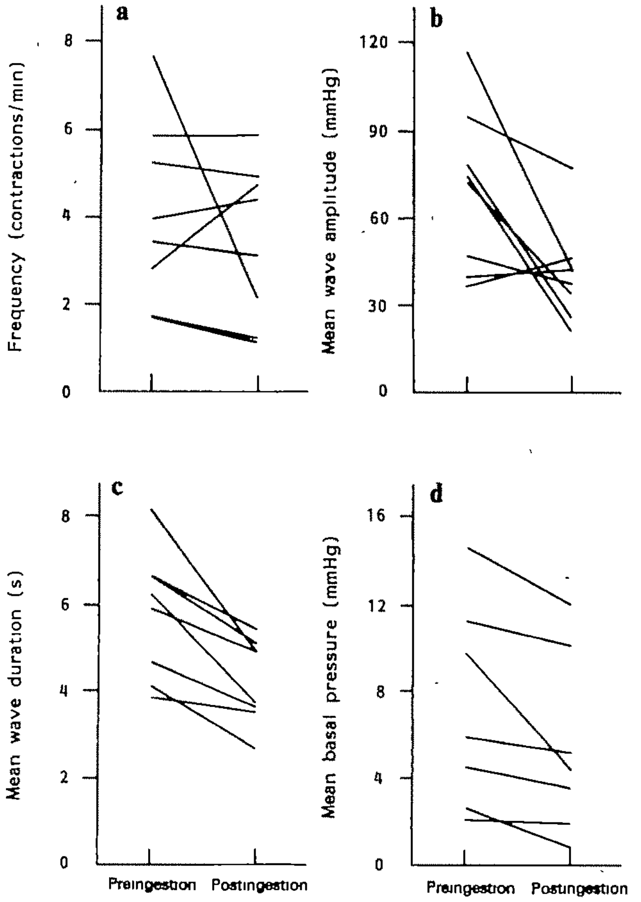

Figure 6 *Comparison of sphincter of Oddi wave* **a** *frequency,* **b** *amplitude,* **c** *duration and* **d** *basal pressure, 10 min before* versus *20 min after food ingestion in eight patients (except for basal pressure where baseline drift excluded data from one patient from analysis). Ingestion of food produced a significant fall in sphincter of Oddi amplitude, duration and basal pressure. There was no change in sphincter of Oddi frequency*

rhythmic contractile activity corresponding to phase III duodenal activity
3. The sphincter of Oddi's rapid contractile activity usually preceded duodenal phase III activity and was of longer duration. Furthermore, the contractile frequency was different in the sphincter of Oddi when compared with the duodenum
4. The sphincter of Oddi basal pressure remained constant throughout the interdigestive cycle except for a brief period during duodenal phase III and early duodenal phase IV
5. After feeding, there was a fall in sphincter of Oddi basal pressure and sphincter of Oddi wave amplitude and duration. There was no change in sphincter of Oddi frequency. Conversely, the duodenum demonstrated a fed pattern with an increase in frequency.

In order to evaluate the interdigestive and fed activity of the sphincter of Oddi in man, patients with indwelling T tubes were used to provide access to the sphincter of Oddi. Neither the T tube modification nor the manometric studies adversely influenced the patients' clinical progress. All of the patients studied were recovering from surgery on the gallbladder and bile duct for stones, hence cannot be considered as having a normal biliary system. Studies in animals[16,17] have shown that cholecystectomy does not alter resting sphincter of Oddi activity. Particular attention was given to avoiding injury to the sphincter of Oddi during surgery, however any effect of the stones in modifying the motility cannot be excluded[13,18]. Furthermore, an effect of the T tube on sphincter of Oddi motility cannot be excluded. In previous studies[13,18] we had shown that stones in the gallbladder or bile duct were associated with an excess of retrograde sphincter of Oddi contractions but no other motility alterations. The significance of these findings with respect to gallstone formation is unknown. In this current study we did not evaluate sphincter of Oddi sequences. However, as best as could be assessed clinically and radiologically, the sphincter of Oddi was otherwise functioning normally.

Particular care was exercised in minimally stimulating the gastrointestinal tract and sphincter of Oddi before and during these studies. We were also conscious of the possibility of producing the complications of pancreatitis and cholangitis due to the placement of the manometry catheter across the sphincter of Oddi and perfusion of the biliopancreatic system; hence the studies were limited to a period of less than 5 h and the system was left open to prevent a pressure build-up. The additional radiation dosage precluded the use of radiological screening to monitor the catheter position continuously.

Prolonged manometric recording during the interdigestive period confirmed findings from a previous study in man[19,20] demonstrating the independence of sphincter of Oddi phasic contractions from duodenal contractions. Unlike duodenal contractions, the sphincter of Oddi contractions were omnipresent and the sphincter of Oddi did not exhibit a period of quiescence. This finding is similar to that reported in the opossum[21,22] and dog[3] and suggests that the sphincter of Oddi contractions may have an important role in maintaining the patency of the bile duct and pancreatic duct by continually expelling fluid from within the sphincter of Oddi segment.

The timing of the sphincter of Oddi activity fronts just before the duodenal phase III has been reported in the opossum[21]. In separate studies we measured human gallbladder volume in relation to duodenal activity and demonstrated that the gallbladder also begins partial emptying just before duodenal phase III activity[23]. These observations were supported by other studies in man which showed a rise in bile salt concentration just before duodenal phase III activity[24,25]. The physiological significance of this inter-relationship between gallbladder contraction and the sphincter of Oddi and duodenal activity fronts is unclear. The difference in timing may reflect the anatomical relationship and have no important physiological connotations. On the other hand, because the gallbladder and sphincter of Oddi activity precedes duodenal phase III, it raises the possibility that an initiator of phase III activity may be sited in the biliary tract. Teleologically it may be argued that an increase in sphincter of Oddi activity should precede duodenal phase III to guard against any reflux of duodenal contents into the bile duct or pancreatic duct which may be generated by the increased activity in the duodenum.

The sphincter of Oddi basal pressure also increased during phase III and into phase IV, which would further guard against reflux during this period of increased duodenal activity. The low sphincter of Oddi basal pressure demonstrated only minor fluctuations throughout the remaining interdigestive cycle, suggesting that normally the sphincter of Oddi does not generate a large resistance to the flow of bile from the duct into the duodenum.

Presentation of food to the patients did not influence sphincter of Oddi or duodenal motility significantly. Our failure to detect a significant change may be because the liquid meal was given only 10 min after presentation of food. If we had waited for a longer period, changes attributable to a cephalic stimulus alone might have been detected.

A nutritionally balanced liquid meal was chosen as the meal stimulus in order to ensure rapid transit from the stomach into the duodenum. We did not objectively monitor the transit of the liquid meal into the duodenum, however we have no cause to believe that any of our subjects suffered from gastric emptying disorders. After the ingestion of the liquid meal, the sphincter of Oddi demonstrated a decrease in wave amplitude with a corresponding decrease in wave duration and a fall in basal pressure. There was no effect on sphincter of Oddi contraction frequency. These changes in activity result, however, from the combination of both the cephalic stimulus and the meal stimulus. The cephalic-induced component of these responses is the subject of further investigation. Other studies in man[7,26] and dogs[27] have shown an increase in flow and corresponding decrease in resistance to flow across the sphincter of Oddi after a meal. Our results suggest that the decrease in resistance across the sphincter of Oddi is produced by this fall in basal pressure and decreased wave amplitude and duration and that the increased flow is facilitated by a passive decrease in resistance and not an active pumping action of the sphincter. This response is different from that seen in opossums, where the response of the sphincter of Oddi to food is a pronounced increase in contractile activity[21,22].

The mechanisms by which these stimuli produced changes in sphincter of Oddi motility were not addressed in this study. Previous studies have shown that an intravenous bolus injection of cholecystokinin octapeptide produced inhibition of sphincter of Oddi phasic contractions[28–31]. The assumption was made that a meal would act on the sphincter of Oddi via the release of endogenous cholecystokinin[32] to produce inhibition of the phasic contractions. This assumption has not been substantiated by our study. Although the amplitude of the phasic contractions has been reduced, total inhibition of the contractions was only transiently recorded in three of our eight subjects. The differences in these observations may be due to the simultaneous release of other hormones after the meal and the interplay between hormonal and neuronal effects on the sphincter of Oddi. Furthermore, the doses of cholecystokinin octapeptide that were used in previous studies may reflect a pharmacological response of the sphincter of Oddi to the stimulus, and not its physiological action.

The results of this study have demonstrated that sphincter of Oddi contractions exhibit a cyclical pattern during the interdigestive cycle. However, unlike the rest of the gastrointestinal tract[33–36], there is no quiescent phase, which may reflect the unique and vital function of the sphincter of Oddi in controlling flow across a very busy anatomical junction. The onset of the sphincter of Oddi activity front precedes that in the duodenum and the sphincter of Oddi basal pressure subsequently increases, suggesting that the sphincter of Oddi inhibits reflux of intestinal contents into the biliary tree during this period of increased duodenal activity. After a meal, passive flow may be enhanced by a fall in the sphincter of Oddi basal pressure and a decrease in the wave amplitude and duration.

Acknowledgements

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Human thrombin plus 5 per cent ethanolamine oleate injected to sclerose oesophageal varices: a prospective randomized trial

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Fifty cirrhotic Japanese patients with oesophageal varices underwent sclerotherapy in a prospective randomized trial carried out to examine the effects of human thrombin given concomitantly with the sclerosant 5 per cent ethanolamine oleate. The two groups (25 patients each) were comparable with regard to size of the oesophageal varices, and the aetiology and severity of the liver disease. Twenty-five patients, 13 and 12 in the thrombin + and − groups, respectively, had at least one episode of variceal bleeding. The remaining 25 were given prophylactic injections. There was a significantly lower rate of occurrence of bleeding from injection sites when the injection needle was removed at the initial session of sclerotherapy in the thrombin + group, where human thrombin was injected (0·2–0·3 ml, 100–150 units per injection) just before removal of the injection needle. Endoscopy at 1 week after the initial session showed a significantly ($P<0{\cdot}05$) *higher rate of disappearance of red colour signs on varices in the thrombin + group (96 per cent) than in the thrombin − group (72 per cent). Fibrin degradation product E-fraction (FDP-E) values increased 1 h, 1 day and 6 days after the initial session of sclerotherapy in the two groups. The rate of increase in FDP-E values 1 h after sclerotherapy was significantly larger* ($P<0{\cdot}001$) *in the thrombin + than in the thrombin − group. There was no clinical sign of disseminated intravascular coagulation. Administration of human thrombin plus a sclerosant seems to be useful and efficacious, especially for patients with huge oesophageal varices.*

Keywords: Injection sclerotherapy, oesophageal varices, 5 per cent ethanolamine oleate, human thrombin

Various compounds have been used[1–5] for endoscopic injection sclerotherapy. Bleeding from injection sites is still one possible major cause of the failure of this treatment because precise injection of the sclerosant may not be attained when the bleeding makes for poor visualization of the varices[6].

A low dose of human thrombin has been injected intravariceally or submucosally to prevent massive bleeding from the puncture points[7,8]; however, the safety of this procedure has not been established.

In the present prospective randomized trial, we compared the findings when we injected 5 per cent ethanolamine oleate plus human thrombin, with 5 per cent ethanolamine oleate only, for patients with oesophageal varices. Particular attention was given to blood coagulability and to the clinical features.

Patients and methods

From December 1987 to April 1988, 50 cirrhotic Japanese patients with histologically proved cirrhosis of the liver (mainly non-alcoholic), portal hypertension and oesophageal varices were randomly allocated to either the thrombin + or the thrombin − group. Randomization was done by flipping a coin for the first of each pair of patients. With informed consent, 25 were given endoscopic injection sclerotherapy, using human thrombin just after each intravascular injection of the sclerosant 5 per cent ethanolamine oleate; for the remaining 25, thrombin was not used. Eight patients presenting acute variceal bleeding during the same period were not included in this study.

Patients with blue varices of a moderate or huge size (F2, F3) and showing either red whale marking (RWM + +, + + +), cherry red spot (CRS + +, + + +) or haematocystic spot (HCS +), were given prophylactic injections according to our criteria[9]. On entering the trial, the patients were classified into grades A, B or C[10].

Treatment was performed using a GIF Q10 Olympus (Olympus Optical Company, Tokyo, Japan) endoscope; the patients were sedated with 5–10 mg diazepam and 15–30 mg pentazocine. Intravariceal injection was initiated approximately 2 cm above the Z-line and was continued in a cranial direction with the free-hand technique, using 5 per cent ethanolamine oleate. The initial two sessions of endoscopic injection sclerotherapy were performed by the principal author (S.K.).

In the thrombin − group, 1·5–2 ml 5 per cent ethanolamine oleate were given per injection; a total of 12–18 ml was injected at the initial session. In the thrombin + group, 0·2–0·3 ml (500 units/ml) human thrombin (Green Cross, Osaka, Japan) was injected intravariceally and submucosally when withdrawing the injection needle and just after giving the 5 per cent ethanolamine oleate injection, in order to prevent massive bleeding from the puncture points.

Repeated sclerotherapy at approximately 1-week intervals was performed until all the oesophageal varices had been eradicated. Sclerotherapy was not repeated when endoscopic findings of the varices showed no definite improvement from the previous session, that is, obliteration of the varices, ulcers or a superficial circumferential ulcer in the lower oesophagus.

The endoscopic features at the first two sessions were recorded. Severity of postinjection bleeding per injection was graded as: jet-like bleeding, continuous bleeding requiring further injections, and no continuous bleeding (ceased within 30 s) from injection sites. At least four of the present authors attended all sessions of sclerotherapy and graded bleeding from the injection sites by observing the endoscopic appearance of the varices through a medical television system (Medical TV System, Model OTV-F2, Olympus Optical Company). To measure blood loss during the procedure, we used a 100-ml glass chamber between the fibreoptic endoscope and the main suction chamber. The blood in the oesophagus was collected through an endoscopic suction channel during the procedure. When there was a small amount of bleeding, blood loss was estimated by the blood concentration in the chamber after flushing with 20 ml saline. The volume of 5 per cent

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Table 1 *Clinical details of patients in the two groups*

	Thrombin + group	Thrombin − group
Number of patients	25	25
Mean age (years)	55·8	56·9
Sex (male:female)	15:10	14:11
Liver function*		
Albumin (g/dl)	3·3 (0·5)	3·3 (0·5)
Total bilirubin (mg/dl)	2·3 (1·2)	1·9 (1·2)
ICG R15 (%)	36·1 (13·8)	36·7 (13·0)
Child's grading[10]		
A	5	7
B	10	11
C	10	9
Selection for sclerotherapy		
Elective	13	12
Prophylactic	12	13
Size of varices[9]		
Moderate (F2)	11	13
Huge (F3)	14	12

* Values are mean (s.d.); statistical analyses were by Student's t and χ^2 tests ICG, indocyanine green test (0–10:normal)

Table 2 *Injections given and severity of bleeding from injection sites at the initial session*

	Thrombin +, group	Thrombin − group	P
Number of injections	9·5 (0·9)	9·6 (2·9)	
Bleeding status (%)			
Jet-like bleeding	0	19 (7·5)	<0·001
Continuous bleeding	6 (6·8)	35 (6·3)	<0·001
Bleeding free	94 (8·8)	46 (7·6)	<0·001
Volume of 5% EO (ml)	15·1 (1·7)	15·6 (2·4)	n.s.
Thrombin (units)	—	1080·0 (322·4)	
Time for sclerotherapy (min)	11·6 (1·4)	15·9 (1·8)	<0·001
Blood loss (>20 ml)	0/25 (0%)	9/25 (36%)	<0·005

Values are mean (s.d.); statistical analyses were by Student's t test except for blood loss (χ^2 test); n.s., not significant; EO, ethanolamine oleate

ethanolamine oleate and human thrombin solution injected, the time taken and the blood loss during the procedure were recorded for subsequent assessment of complications and efficacy. Particular attention was directed to coagulability status after the initial session of sclerotherapy The platelet count, prothrombin time, partial thromboplastin time and fibrinogen and fibrin degradation product E-fraction (FDP-E) of each patient were analysed in the early morning before sclerotherapy. Repeat measurements of haematological parameters were made 1 h, 1 day and 6 days after the completion of the initial session.

The variables of interest were compared using either the χ^2 test or Student's t test.

Results

Characteristics of the two groups

Table 1 shows the clinical characteristics of the patients studied. The two groups were well matched for all variables. Thirteen patients in the thrombin + group and 12 in the thrombin − group were treated, on an elective basis, 3–28 days after their latest episodes of variceal bleeding. Prophylactic injection was given to 12 patients in the thrombin + and 13 in the thrombin − group, as the endoscopic findings showed a risk of bleeding. There were eight patients with a concomitant hepatoma (four in each group), lesions which were not resectable for functional and/or anatomical reasons (poor liver function, huge or multiple hepatomas).

Endoscopic features at the initial session (Table 2)

Jet-like bleeding from an injection site occurred in 19 per cent of cases with a mean of 9·6 injections in the thrombin − group, but this type of bleeding never occurred in the thrombin + group. The difference was statistically significant ($P<0·001$). There was also a significant difference ($P<0·001$) in the frequency of bleeding-free injections between the two groups, 94 *versus* 46 per cent in the thrombin + and thrombin − groups, respectively.

Time and blood loss (>20 ml) during the procedure were significantly shorter in the thrombin + group than in the thrombin − group, and the total volume of 5 per cent ethanolamine oleate injected was comparable in the two groups. There were nine patients who lost more than 20 ml of blood during the procedure in the thrombin − group, whereas there were none in the thrombin + group, the difference being statistically significant ($P<0·005$). In patients with F3 (huge and nodular form) varices, there was a higher rate (seven of 12, 58 per cent) of bleeding from injection sites than in the patients with F2 (moderate and rosary) varices (two of 13, 15 per cent).

Endoscopic findings 1 week after the initial session

Table 3 shows endoscopic findings 1 week after sclerotherapy. In 24 of the 25 patients in the thrombin + group, the oesophageal mucosa over the varices where the sclerosant had been injected was thick and swollen, presumably the effect of thrombosis and inflammation resulting in disappearance of red colour signs on varices. In the thrombin − group, the oesophageal varices were endoscopically patent and showed a considerable degree of red colour signs in seven of 25 patients, the difference being statistically significant (96 *vesus* 72 per cent, $P<0·05$). In accordance with endoscopic findings, continuous bleeding from injection sites requiring further injection at the second session occurred more frequently in the thrombin − group (30 per cent of an average of 9·2 injections) than in the thrombin + group (9 per cent of an aveage of 8·6 injections), the difference being statistically significant ($P<0·05$). Occurrence of oesophageal ulceration 1 week after the initial session was significantly ($P<0·05$) more frequent in the thrombin − group than in the thrombin + group.

Number of sessions, period, and volume of the sclerosant

The number of sessions, weeks of treatment and total volume of 5 per cent ethanolamine oleate for eradication of oesophageal varices did not differ between the two groups, as shown in *Table 4*. At the late stage of repeated injections, the residual mucosa was partly necrotized and eliminated with submucosal spread of the sclerosant and the mucosa remained, despite the

Table 3 *Endoscopic findings 1 week after the initial session*

Findings	Thrombin + group ($n=25$)	Thrombin − group ($n=25$)	P
Disappearance of red colour signs	24 (96)	18 (72)	<0·05
Slough and/or ulcer formation	1 (4)	6 (24)	<0·05

Values in parentheses are percentages; statistical analysis was by χ^2 test

Table 4 *Number of sessions, weeks of treatment and total volume of 5 per cent ethanolamine oleate for variceal eradication*

	Thrombin + group	Thrombin − group	P
Number of patients	25	25	
Size of varices (F2:F3)	11:14	13:12	n.s.
Sessions	5·4 (1·0)	5·0 (1·1)	n.s.
Weeks	5·6 (1·2)	5·8 (1·2)	n.s.
Total volume of 5% EO (ml)	49·4 (12·7)	49·7 (11·3)	n.s.

Values are mean (s.d.); statistical analyses were by Student's t test except for variceal size (χ^2 test); n.s., not significant; EO, ethanolamine oleate

Table 5 *Alteration of parameters of the coagulating system before and after injection sclerotherapy in the two groups*

	Thrombin + group			Thrombin − group		
Parameters	Before	After day 1	After day 6	Before	After day 1	After day 6
PT (%)	72·6 (22·8)	63·8 (18·7)	65·6 (13·3)	71·3 (22·7)	78·3 (16·0)	75·3 (20·6)
PTT (%)	36·8 (5·4)	38·2 (6·3)	37·3 (4·1)	37·7 (6·5)	36·3 (5·2)	37·8 (7·7)
Fibrinogen (mg/dl)	211·0 (80·7)	223·6 (82·8)	236·8 (59·8)	225·8 (73·2)	238·6 (71·3)	259·5 (61·9)
Platelets ($\times 10^4$)	7·4 (2·8)	7·2 (2·4)	7·9 (2·9)	7·9 (3·3)	8·9 (3·9)	9·2 (5·1)
FDP-E (ng/ml)	103·3 (82·7)	252·3* (191·5)	199·4* (94·2)	92·5 (78·8)	210·2* (103·1)	245·4* (85·0)

Values are mean (s.d.). PT, prothrombin time; PTT, partial thromboplastin time; FDP-E, fibrin degradation product – E fraction; * $P<0·001$ compared with the values before sclerotherapy (Student's *t* test)

Table 6 *Fibrin degradation product values before and 1 h after completion of the initial session of sclerotherapy*

FDP-E level (ng/ml)	Thrombin + group ($n=25$)		Thrombin − group ($n=25$)	
	Before	After	Before	After
0–100	16	0	17	3
100–500	9	7	8	22
>500	0	18	0	0
Mean (s.d.)	103·3 (82·7)	1982·3* (1638·7)	92·5 (78·8)	214·8* (132·1)

FDP-E, fibrin degradation product E-fraction; * $P<0·001$ compared with the values before sclerotherapy (Student's *t* test). the increase was significantly ($P<0·001$) larger in the thrombin + group

administration of a sufficient volume. The rate of attainment of a superficial circumferential ulcer formation (our proposed end-point) in the lower oesophagus[11] did not differ between the two groups, 64 *versus* 56 per cent in the thrombin + and − groups, respectively.

No patient died during the course of repeated injections and all could be given a sufficient number of sessions. One patient in each group died of a concomitant hepatoma 4 and 5 months after the initiation of therapy. At the time of writing, 24 patients in each group are living with no episode of bleeding.

Alteration of parameters of the coagulating system

There was a significant increase in FDP-E 1 day after the initial session in both groups (*Table 5*), while the other parameters showed no significant increase. The value of FDP-E remained significantly high for the following week ($P<0·001$). The increase in FDP-E was significantly ($P<0·001$) larger in the thrombin + group than in the thrombin − group 1 h after completion of the first session: 19·8 × *versus* 2·4 ×, compared with the pre-injection values (*Table 6*). Four patients of the thrombin + group showed a markedly high value in FDP-E level (more than 4000 ng/ml), without presenting clinical signs of bleeding tendency or intravascular coagulation throughout the course of repeated sclerotherapy.

Complications

There were no major complications, such as oesophageal perforation or shock, directly related to the procedure or injection of a low dose of human thrombin, except for the previously mentioned haematological abnormalities. Oesophageal bleeding did not occur during the entire course of repeated injections. There was no statistically significant difference in the frequency of minor complications between the two groups: pain requiring opiate analgesics in 8 per cent of the thrombin + and 12 per cent of the thrombin − group; pyrexia (>38°C) in 32 and 40 per cent respectively; and pleural effusion on chest X-ray in 40 and 48 per cent, respectively. Oesophageal stricture which required bougienage occurred in three and four patients of the thrombin + and − groups, respectively.

Discussion

Since the first report by Crafoord and Freckner[1], various agents have been used to sclerose oesophageal varices. In our prospective randomized clinical trials[12,13], 5 per cent ethanolamine oleate was found to be superior to 1 per cent polidocanol or 2 per cent sodium tetradecyl sulphate. In canine models[14] with portal hypertension, Jensen *et al.* found that 5 per cent ethanolamine oleate proved to be the most efficacious single agent for sclerosing oesophageal varices, with a low rate of occurrence of oesophageal ulceration after the injection.

Many workers performed endoscopic injection sclerotherapy with a free-hand technique, under conditions of topical anaesthesia. However, recurrent bleeding or continuous bleeding from the injection site is still a major cause of failure of sclerotherapy, especially at the very early stage[5,6,15].

Some investigators favoured the use of a low dose of human thrombin together with other sclerosants[7,8,16], the objective being to prevent massive acute bleeding and to obtain accurate visualization. In the present study, we confirmed that use of a low dose of human thrombin makes injection sclerotherapy an easier technique to perform as the view of the varices is not obscured by bleeding.

Gardner and Brooks[7] reported no definite evidence of disseminated intravascular coagulation after intravariceal injection of 5 per cent sodium morrhuate and a solution containing thrombin. Bernardie *et al.*[17] suggested that 5 per cent ethanolamine oleate caused no significant deterioration of coagulation, even in patients with an abnormal coagulative function, and that temporary activation of the coagulating process might be self-limiting and confined to the laboratory level. In our present study, the serum level of FDP-E was higher than the normal limit for at least the first week in all patients given an injection of 5 per cent ethanolamine oleate, even after the other parameters had recovered to the pre-sclerotherapy level. The additional use of human thrombin after each injection of 5 per cent ethanolamine oleate caused a significantly higher increase in the FDP-E level than did 5 per cent ethanolamine oleate alone Much more attention should be directed to this higher FDP-E level increase

(>4000 ng/ml) seen in four patients injected with human thrombin (750–1250 units) intravariceally and submucosally. These high values suggest that cirrhotic patients are in a predisseminated intravascular coagulation state even before injection and that such a state may readily occur after intravariceal injection of human thrombin, even though sclerotherapy can be performed with little bleeding.

Larger varices tend to bleed more during the procedure To prevent active and massive bleeding from the injection sites, low dose human thrombin is an effective agent. Nevertheless, injection of 5 per cent ethanolamine oleate led to deterioration in the coagulation system and the additional use of human thrombin caused a further deterioration of the coagulation system in patients with liver cirrhosis.

On the basis of this trial, we recommend that low dose human thrombin is used, with the free-hand technique, to prevent bleeding from injection sites and to obtain a complete thrombosis of variceal channels in patients with large oesophageal varices, otherwise active bleeding may occur just after the intravenous injection of the sclerosant. Close follow-up is necessary to predict and prevent the occurrence of true disseminated intravascular coagulation.

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Rigid endoscopy under general anaesthesia is safe for chronic injection sclerotherapy

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Injection sclerotherapy for acutely bleeding oesophageal varices has been used in Belfast since 1958. However, a chronic injection sclerotherapy programme with rigid oesophagoscopy under general anaesthesia commenced only in 1979. So far, 82 patients have entered the programme; 57 patients had already received 73 acute injections before commencing chronic sclerotherapy. Subsequently, the 82 patients received 221 chronic injections plus a further 29 acute injections for rebleeding episodes which occurred during the programme. There were 24 Child's grade A patients, 23 B and 35 C; 48 per cent had alcoholic cirrhosis. Forty-eight patients achieved variceal obliteration with a mean of four injections. During the programme 24 patients experienced 42 acute bleeds. There were only two bleeding episodes within 1 week of a chronic injection and eight within 4 weeks. In the 8-year period there have been four early deaths. One occurred 17 days after a chronic injection and three followed acute injections required for rebleeding during the programme. There were 21 late deaths, mostly due to progressive liver failure, and none from rebleeding. We conclude that chronic injection sclerotherapy using rigid oesophagoscopy under general anaesthesia is both safe and effective.

Keywords: Injection sclerotherapy, oesophageal varices, rigid oesophagoscopy, general anaesthesia

The first report[1] of the use of injection sclerotherapy for bleeding oesophageal varices was published in 1939. Injection sclerotherapy for acutely bleeding oesophageal varices has been used in Belfast[2] since 1958. A previous report from this unit reviewed 25 years of experience of injection sclerotherapy for acute bleeding from oesophageal varices[3]. This gave a control rate of 91·4 per cent with a mortality rate of 14·9 per cent. After the acute episode, some regimen of definitive therapy is necessary to prevent recurrent variceal haemorrhage. Medical therapy using propranolol[4–7], shunt surgery[8–12], oesophageal transection[13,14] and chronic injection sclerotherapy[15–18] have all been used. A chronic injection programme commenced in Belfast in 1979 and this paper reviews our results Most authorities advocate the use of a flexible endoscope with or without an oversheath for chronic injection. In our programme, rigid oesophagoscopy and general anaesthesia were used for both acute and chronic injections. This resulted in minimal operative mortality and morbidity and a high rate of variceal obliteration.

Patients and methods

Patients

Eighty-two patients entered the programme between January 1979 and October 1987 There were 39 men and 43 women in the series. The age ranged from 17 to 83 years with a mean of 52·9 years Severity of liver disease upon entering the programme was assessed using Pugh's modification of Child's grading. There were 24 grade A (30 per cent), 23 grade B (28 per cent) and 35 grade C patients (42 per cent).

Most of our patients selected for chronic sclerotherapy were those considered unfit or unsuitable for surgery. However, 11 good-risk patients were entered as part of a random group in a multicentre chronic injection sclerotherapy trial. Another five good-risk patients were deliberately selected because their underlying pathology was extrahepatic venous obstruction. No patient was rejected from the programme because of poor liver function.

The aetiology of the portal hypertension is shown in *Table 1*. Patients without evidence of alcohol abuse, other causes of intrahepatic portal hypertension or extrahepatic venous obstruction were included in the cryptogenic group. Just over 50 per cent of our alcoholic cirrhotics became total abstainers

Injection technique

Anaesthesia is induced with thiopentone and paralysis achieved with suxamethonium Maintenance of anaesthesia is by 70 per cent nitrous oxide with oxygen or isoflurane.

The 50-cm wide bore rigid Negus oesophagoscope and long Roberts needle are used. Occasionally the narrower instrument is employed for technical reasons. From 2 to 4 ml of ethanolamine oleate are injected intravariceally into each varix Only the varices in the distal 5 cm of the oesophagus are injected. The oesophagoscope is rotated to compress the previous injection site while injecting a further varix. Postinjection tamponade was not used in any patient

Results

The 82 patients received a total of 323 injections of which 221 were chronic and 102 acute. Of the acute injections, 73 had been given to 57 patients before commencing the chronic injection programme; the other 29 were for acute bleeding during the programme. Although all 82 patients had bled before entering the programme, 25 had not required emergency sclerotherapy

Table 1 *Aetiology of portal hypertension*

	n	%
Alcoholic cirrhosis	39	48
Cryptogenic cirrhosis	19	23
Primary biliary cirrhosis	8	10
Chronic active hepatitis	6	7
Portal vein thrombosis	5	6
Miscellaneous	5	6
Total	82	

Table 2 *Cause of mortality during programme*

Total deaths	25
Progressive liver failure	17 (13 Child's C)
Unrelated to liver disease	8 (4 Child's C)
Renal failure	1
Gunshot wounds	1
Carcinomatosis	1
Mesenteric infarction	1
Bronchopneumonia	1
Subarachnoid haemorrhage	1
Peroperative haemorrhage	1
Fulminant ulcerative colitis	1

Treatment regimen

Chronic injection sclerotherapy was the only treatment used in 55 of our 82 cases. Seven patients left the programme and underwent an elective oesophageal transection. Secondary chronic injection sclerotherapy was required for variceal recurrence in a further 20 patients who had had prior transection (18 patients) or shunt (two patients).

Variceal obliteration

Of the 82 patients entering the programme, 48 have so far achieved variceal obliteration. Of these, 34 are still alive and 14 have died, mostly from progressive liver failure. This leaves 34 patients who have not achieved variceal obliteration: 11 died before obliteration was considered to have been achieved, and 23 are still alive, currently in our ongoing programme, and should soon achieve obliteration of their varices. The 48 patients with obliterated varices required a total of 192 injections. This ranged from one to ten, and the mean number of injections required was 4·0. After variceal obliteration, endoscopic review using the flexible instrument is performed annually.

Variceal bleeding

In the very early stages of our programme, there was no rigid schedule of timing of chronic injections. Consequently, some patients received their first chronic injection more than 1 month after their initial acute injection. The gap between chronic injections also varied, and was occasionally longer than 3 months. We soon adopted a schedule of chronic injection 1 month after the initial acute injection and then repeated at monthly intervals. There were a total of 42 episodes of variceal rebleeding in 24 patients after commencing the programme. In five of these patients the bleeding site was non-variceal. These included hiatal hernias with oesophagitis, gastric erosions, prepyloric ulceration and duodenal erosion. In the 19 patients bleeding from varices, 29 of the bleeding episodes required acute injection sclerotherapy. Two episodes occurred within 1 week of a chronic injection, three by 2 weeks, three by 4 weeks, thirteen within 12 weeks, and the remainder after this period. The incidence of rebleeding has decreased since patients began routine monthly chronic injections.

Complications

The 82 patients received a total of 221 chronic injections under general anaesthesia. One Child's grade C patient died from progressive liver failure after a chronic injection. One patient had a minor cervical oesophageal leak which settled with conservative management. One of the advantages of a general anaesthetic is the safe airway, and there was only one case of aspiration pneumonitis. There were no episodes of unsuccessful intubation and no morbidity or mortality could be attributed to the general anaesthetic. Oesophageal ulceration was noted in only two patients and none of the 82 patients subsequently developed an oesophageal stricture. In the first 48 h, a pyrexia of up to 38°C occurred in about 20 per cent of patients. Mild retrosternal pain was experienced by about 35 per cent of patients.

Mortality

In the 8-year period under review there was a total of 25 deaths in the 82 patients (*Table 2*). Four of these deaths occurred in hospital, related to injection sclerotherapy. As mentioned earlier, one hospital death occurred 17 days after a chronic injection and was due to progressive liver failure in a Child's C patient. The other three hospital deaths (two Child's B, one Child's C) occurred at 12, 20 and 25 days respectively, after acute sclerotherapy for rebleeding episodes. These deaths were all due to liver failure.

Discussion

The prevention of recurrent haemorrhage from oesophageal varices is a controversial topic. Proposed regimens include medical therapy, injection sclerotherapy and operative treatment such as shunting or oesophageal transection.

Chronic injection sclerotherapy has received increasing attention in recent years. The combined results of three prospective controlled studies involving 173 patients showed that a chronic injection programme is effective[15–17]. The number of patients rebleeding fell from 67 to 52 per cent and the number of rebleeding episodes was almost halved. Terblanche showed that survival in a group undergoing chronic injection was unchanged compared with a control group[16]. This control group, however, did receive acute injections for rebleeding episodes. The rate of admission for rebleeding was decreased from 77 to 58 per cent, making life less traumatic for both patients and surgeon. In this series only 29 per cent of the patients experienced any bleeding episodes during the programme and not all of these were due to varices.

There is controversy over the best injection site for sclerotherapy, the correct timing and the most suitable instrument. Intravariceal injection produces a more rapid obliteration of varices than the paravariceal route. Rose *et al.*, comparing the two, showed a more rapid reduction in variceal size and a significant reduction in the number of injection sessions required with intravariceal injection[19]. Another study showed that intravariceal sclerotherapy was superior to paravariceal in the control of active variceal bleeding and for total obliteration of varices, but was associated with a higher variceal recurrence rate[20].

The timing of injection has been assessed by the King's College Hospital Group, who found that sclerotherapy performed at intervals of <3 weeks increased the complication rate but resulted in earlier variceal obliteration[21]. Sarin *et al.* found that weekly rather than 3-weekly injections gave both earlier obliteration and decreased rebleeding[22]. They judge the greatly increased incidence of mucosal ulceration with earlier injection to be inconsequential. We feel that a monthly injection regimen permits oedema, mucosal inflammation and any ulceration to resolve before any further injection. In our experience the incidence of rebleeding within the first month of the initial sclerotherapy has been very low – only eight episodes in the whole series.

Rigid oesophagoscopy gives better visualization than flexible oesophagoscopy, permitting more accurate intravariceal injection of lower volumes of sclerosant. Intravariceal injection is aided by the venous distension produced by the rigid instrument. Haemorrhage is controlled by compression, which also traps the sclerosant in the varix, aiding sclerosis. The main disadvantage of rigid oesophagoscopy is said to be the risk of perforation. We had only one minor cervical perforation in 221 chronic injections in our 82 patients. Our method achieved a very low rate of ulceration and no postinjection stenosis. The rate of mucosal ulceration observed in one study was 80 per cent for a weekly injection regimen and 33 per cent for a 3-weekly injection regimen[18]. We noted only two instances of ulceration in 82 patients (2 per cent). This figure is falsely low because of our decreased frequency of endoscopy compared with other series. It may also reflect the value of accurate intravariceal injection and lower volumes of sclerosant. None of our 82 patients subsequently developed an oesophageal stricture. This compares very favourably with stricture rates of 17·6 per cent using 3-weekly flexible endoscopy[15] and 8·5 per cent using weekly flexible endoscopy[22], both under sedation. Howard *et al.*, who employed general anaesthesia but differed from us in using flexible endoscopy[23], had a stricture rate of 16 per cent. Perhaps it is worth noting that in 30 years of injection sclerotherapy with the rigid oesophagoscope we have seen only two minor strictures in over 800 injections in more than 400 patients.

The most controversial aspect of this review is the need to use general anaesthesia for a chronic injection programme using the rigid instrument. However, a general anaesthetic safeguards the airway, prevents aspiration of blood and maintains good oxygenation throughout the procedure. In addition, recovery is quicker than with sedation and many patients prefer to be fully asleep, an important factor in patient compliance. Howard *et al.* also defend the use of general anaesthesia in their large series of 152 children and teenagers with oesophageal varices[23]. The main disadvantage is the extra 24 h required as an in-patient.

Most authorities advocate flexible endoscopy under sedation for chronic sclerotherapy. The Cape Town controlled trial comparing rigid and flexible oesophagoscopy showed no difference in morbidity or mortality[24]. It is accepted that either rigid or flexible endoscopy may be used for a chronic sclerotherapy programme depending on the preference and expertise available. Most importantly, the operator must be proficient in whichever technique is practised. While we do not advocate the routine use of rigid endoscopy, we do defend its use in centres experienced in the technique. Our results show that chronic injection sclerotherapy using rigid oesophagoscopy under general anaesthesia is both safe and effective.

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Emergency orthotopic liver transplantation in two patients using one donor liver

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Because of its anatomy, the liver can be divided into two hemilivers suitable for use as two grafts for liver transplantation. The line of division is the main scissure, giving the right hemiliver (segments 5–8) and the left hemiliver (segments 2–4). Segment 1 (caudate lobe) has to be resected. The vessels are divided between the two grafts: the vena cava remains on the right; on the left, the left hepatic vein is sutured into the vena cava of the recipient, which is retained intact. The left graft retains only the left branch of the portal vein, the bile duct and the hepatic artery. The right graft retains the portal trunk, the common bile duct and the right branch of the hepatic artery. This procedure was used for emergency grafting of two patients with fulminant hepatitis when only one donor was available. Both recipients recovered from coma and regained normal liver function. However, both died from causes not specifically related to the operative technique, one from multiple organ failure on the 20th day and the other from diffuse cytomegalovirus infection on the 45th day.

Keywords: Liver transplantation, partial graft, live donor

In 1978, we started a programme of emergency heterotopic liver transplantation for patients with end-stage cirrhosis, using only a portion of the donor liver in order to have room in the abdomen for the transplant[1]. In 1983, the same technique of graft reduction was used in children for orthotopic transplantation[2] and, in 1986, it was used for emergency transplantation for fulminant hepatitis[3]. In this reduced-sized liver, the entire vena cava and the portal pedicle are retained, and vascular and biliary reconstruction are the same as in the usual orthotopic liver transplantation. A partial liver graft[4] (often improperly called a segmental graft) is different in that only some of the branches of the major vessels of the portal pedicle and of the vena cava are used. In this report we describe the use of one donor liver for two orthotopic transplantations by dividing the liver to obtain functional livers for each of two patients with fulminant hepatitis.

Patients and methods

A 45-year-old woman with fulminant hepatitis of indeterminate cause was admitted on 1 May 1988. She was comatose, with inco-ordinate response to nociceptive stimuli (grade III coma). Her biochemical tests showed: serum bilirubin 380 μmol/l, serum alanine aminotransferase 980 units/l, prothrombin 10 per cent of normal, and serum creatinine level 95 μmol/l. The only available donor was in Bern, Switzerland. Biochemical tests on the donor revealed: serum bilirubin 5 μmol/l, serum alanine aminotransferase 42 units/l, γ-glutamyl transpeptidase 400 units/l, and prothrombin 60 per cent of normal. Multiple organs were harvested, with infusion of the kidneys and the liver with University of Wisconsin solution[5]. The weight of the liver was 2·6 kg. As the hepatectomy on the recipient was started, however, a 55-year-old woman with drug-induced fulminant hepatitis was admitted. She was diabetic and had a history of arterial hypertension. On 13 April she had become jaundiced and her serum alanine aminotransferase was 700 units/l. On admission, she was comatose (grade III), anuric and was receiving mechanical ventilation. Her biochemical tests were serum bilirubin 420 μmol/l, serum alanine aminotransferase 420 units/l, prothrombin 12 per cent of normal, and serum creatinine level 350 μmol/l. The preoperative blood cultures and culture of ascitic fluid were positive for *Escherichia coli* and *Enterobacter cloacae*. We decided to modify the surgical procedure to obtain two functional hemigrafts for the two patients.

Technique of division of the liver graft (Figure 1)

After the usual *ex vivo* preparation of the graft, the liver and the hepatic pedicle were divided into two parts. The left hemigraft consisted of the left liver (segments 2–4), the left hepatic duct, the left branch of the portal vein, and the complete hepatic artery from the coeliac axis but without the right branch. The hepatic veins consisted of the left hepatic vein and an accessory middle hepatic vein (with a common opening) with a small cuff of vena cava. The surface of the left hemigraft was covered with a fibrin glue (Tissucol-Immuno Ag, Vienna, Austria).

The caudate lobe of the right hemigraft was resected because it received its portal blood supply from the left portal branch (taken with the left graft). The right hemigraft consisted of the right liver (segments 5–8) with the portal vein in continuity with the right portal branch, with the right branch of the hepatic artery, and with the common bile duct in continuity with the right hepatic duct. The hepatic veins of the right liver consisted of the right and the middle hepatic veins and the vena cava. The cut surface of the hemigraft was covered with fibrin glue. Preparation of the two hemigrafts took 2 h 30 min.

Liver transplantation in the first patient

Because this patient was smaller than the second, she received the left hemigraft. Her liver was removed, conserving the vena cava. The orifices of the left and middle hepatic veins were sutured to the small cuff of the vena cava of the donor with the two hepatic veins. The left portal branch of the hemigraft was sutured to the portal vein of the recipient. After portal revascularization of the graft, the coeliac axis of the graft was sutured to the common hepatic artery of the recipient. Finally, because of the lack of length of the left bile duct, it was anastomosed to a Roux-en-Y loop of jejunum. Flow in the intrahepatic vessels was assessed by Doppler ultrasound. The graft had been ischaemic for 7 h 50 min.

Liver transplantation in the second patient

This transplantation started before the end of the first procedure. Total hepatectomy was accomplished according to the usual technique. The only technical variation concerned the hepatic artery, which was completely dissected to keep its right branch. This branch was sutured to the right hepatic arterial branch of the recipient. The biliary tract was reconstructed by an end-to-end suture of the common bile duct of the graft and of the recipient over a T tube. The graft was ischaemic for 12 h 50 min. The surgical procedure on the two patients lasted 16 h.

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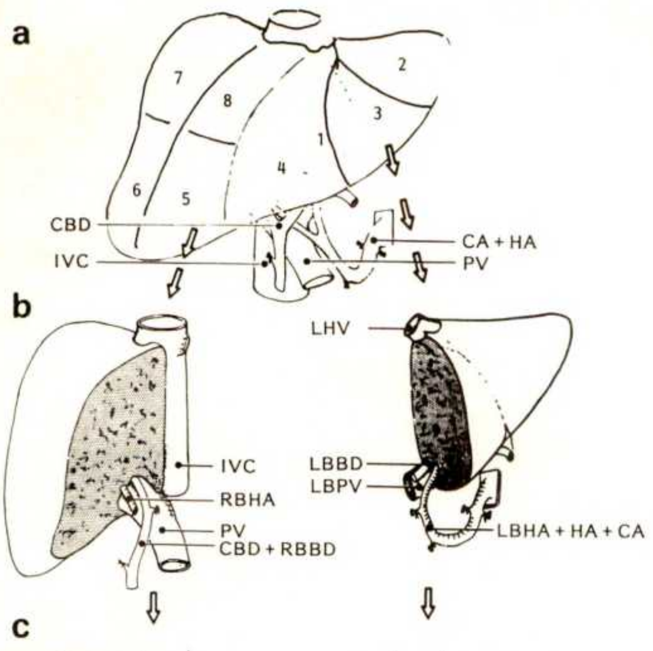

Figure 1 *Technique of division of the donor liver to obtain two functional hemigrafts.* **a** *The segments and major structures of the entire normal liver are labelled;* **b** *division of the liver into two hemigrafts: right hemigraft (segments 5–8) and left hemigraft (segments 2–4);* **c** *implantation of the hemigrafts. IVC, inferior vena cava; PV, portal vein; CBD, common bile duct; CA, coeliac axis; HA, hepatic artery; RBHA, right branch of hepatic artery; RBBD, right branch of bile duct; LBBD, left branch of bile duct; LBPV, left branch of portal vein; LBHA, left branch of hepatic artery; LHV, left hepatic veins; BBA, biliobiliary anastomosis; BJA, biliojejunal anastomosis.*

Results

Postoperative course of the first patient

The first patient regained consciousness completely 36 h after surgery and was extubated on the second day. On the following days, the liver function tests returned to normal. The patient was discharged from the intensive care unit on the eighth day. The postoperative course was uneventful until the 22nd day, when the patient developed a diffuse cytomegalovirus infection; she died of pneumonitis on the 45th day. At the post-mortem examination, the liver parenchyma appeared homogenous; all the vascular and biliary anastomoses were patent and there was a massive haemorrhagic infiltration of the lungs which was responsible for death.

Postoperative course of the second patient

The haemodynamic condition of the patient remained poor. She was reoperated on for haemoperitoneum on the second day and again on the fifth day. The serum levels of aspartate aminotransferase reached 4600 units/l on the second day, then returned progressively to normal; her prothrombin time returned to 60 per cent of normal on the third postoperative day. She regained consciousness completely but continued to require mechanical ventilation. The postoperative course was complicated by the persistence of renal failure requiring repeated haemodialysis, the development of disseminated intravascular coagulopathy, and sepsis due to *Candida albicans*. The patient died from multiple organ failure on the 20th postoperative day. At the post-mortem examination, the liver parenchyma appeared homogenous; all the vascular and biliary anastomoses were patent.

Discussion

Because we needed to perform two emergency transplantations simultaneously when only a single donor was available, we divided one graft to perform two transplantations. Pichlmayr and his co-workers have recently published a similar report[6], using one liver for an adult, who received the right liver plus segments 1 and 4, and for a child, who received the left lateral surgical sector (segments 2 and 3). Even though both patients discussed in our report died, the causes were not specifically related to the operative technique or failure of the graft. The graft function in the first patient was satisfactory as she regained consciousness completely, with a normal prothrombin level, after the second postoperative day. The graft function in the second patient was more difficult to assess as she was in septic shock before, during and after the surgical procedure. However, despite her poor haemodynamic condition, the graft function was satisfactory, as she regained consciousness completely with disappearance of jaundice and a prothrombin level at 60 per cent of normal after the third postoperative day. The best proof of good function of the two grafts is the fact that the two patients, transplanted in a deep coma, regained complete consciousness immediately after the operation. However, more experience and better results are needed before this technique is applied to indications other than emergency situations.

The anatomy of the liver[7] makes possible the use of one divided liver for two transplants. The line of division of the right and left livers runs between segments 5 and 8 on the right and segment 4 on the left. It was preferable to excise the caudate lobe (segment 1), which receives its portal and arterial branches mainly from the left portal pedicle and is drained by small hepatic veins going directly to the vena cava. In our operation, because the left lobe (segments 2 and 3) seemed to be small, the quadrate lobe (segment 4) had to be conserved. Conservation was possible by the presence of an accessory middle hepatic vein for the quadrate lobe[7]. The division of the portal vein and the biliary tree presented no difficulty: the left branches of these two structures being longer than the right, it was better to use them and to keep the portal trunk and the common bile duct in continuity with the right hemigraft. The frequent anatomical variations of the hepatic artery necessitated its division. Although it would have been preferable to perform coeliac arteriography, the anatomy of the portal branches and of the arteries can be studied *ex vivo* by exploring the vessels with a probe. Intraoperative ultrasound, so helpful in studying the anatomical variation of the vessels, could not be applied here because of the presence of the preservation solution and the small bubbles that it contained.

The use of the University of Wisconsin solution makes the procedure easier and more reliable. The hepatic graft has a softer consistency when it is infused with University of Wisconsin solution than with Collins solution, making division of the liver easier. Also, use of the University of Wisconsin solution permits prolonged ischaemic time[5].

The present procedure is an improvement when compared with the reduced-sized graft we described previously, where the remaining liver could not be used for grafting. The 'one for two' procedure and the University of Wisconsin solution should open new possibilities in liver transplantation. For instance, if an emergency liver transplantation is performed with a partial liver graft, the second liver could be used for a patient on the waiting list, chosen according to the anatomical features of the remaining hemigraft. The left hemigraft could be used, preferably in a child (if necessary, reduced to segments 2 and

3 by removing the quadrate lobe), and the larger right hemigraft for an adult. In any case, as it is feasible to use small grafts in adults, one liver could be used for two transplants in order to overcome the shortage of liver grafts.

Another consequence of this technique is the possibility of using a live donor. In this situation, the liver graft would be a partial graft, as we used in our first patient. The only technical difference would pertain to the hepatic artery; however, preoperative angiography could allow one to take only a branch of the hepatic artery. Currently, the only possibly acceptable indication for the use of a live donor for liver grafting would be encountered in a patient dying from fulminant hepatic failure with no other donor available.

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Timing of strangulation in adult hernias

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This retrospective study aimed to determine why the incidence of strangulated hernias in adults remains high. Seventy-nine patients presented with clinical evidence of hernia strangulation which required urgent surgery during the period 1979–87. Forty-six patients (58 per cent) had noted a hernia present for at least 1 month before strangulation: 18 (23 per cent) had not reported it to their family doctor, 19 (24 per cent) were known by family practitioners or non-surgical medical personnel to have a hernia but had not been referred for surgical opinion, and nine (11 per cent) had been previously assessed surgically with a view to elective repair. Of these nine, five were considered unfit, three were on waiting lists for operation and one had refused surgery. Thirty-two patients (40 per cent) presented primarily with strangulation within days of developing a hernia. The duration of hernia before strangulation in one patient was unknown. Although an unavoidable number of patients will continue to present with strangulation within days of developing a hernia, the overall incidence could be significantly reduced by greater public awareness of the risks of hernia strangulation and by a policy of immediate patient referral and prompt elective repair.

Keywords: Hernia, strangulation, timing, surgery

Despite universal acceptance of the value of elective hernia repair[1], the number of patients presenting with strangulation remains high[2–3]. It has recently been suggested that many of those patients who present with strangulation are elderly and are on waiting lists for hernia repair but surgery is delayed or denied them because surgeons and practitioners are exercising a selective policy in favour of younger patients with fewer operative risk factors[3]. This retrospective study analyses the spectrum of strangulated hernias in adults and focuses particular attention on the duration and management of such hernias before strangulation.

Patients and methods

Seventy-nine adult patients (over 20 years of age) who required emergency surgery for suspected strangulated hernia during the period 1979–87 are included in the study Age, sex, site of hernia, coexistent medical illness, operative procedure performed and duration of postoperative stay were recorded. The duration of the hernia before strangulation and any previous hospital admissions during which the hernia had been noted were also recorded Previous visits by the patient to the family practitioner regarding the hernia or during which the hernia was noted were recorded from the case notes or the practitioner concerned

The hernia sites included: 37 femoral (21 right sided), 33 indirect inguinal (19 right sided), five paraumbilical, two incisional, two epigastric and one obturator. One patient developed a strangulated right femoral hernia followed 1 month later by a strangulated femoral hernia on the other side.

Results

Age and sex distribution are outlined in *Figure 1*. The peak incidence for strangulation occurred in the seventh decade of life

The history of presence of a hernia before strangulation is outlined in *Table 1*. Forty-six patients (58 per cent) had noticed a hernia present for at least 1 month before strangulation: 18 (23 per cent) had not reported it to their family doctor (12 inguinal, four femoral, one epigastric, one paraumbilical), ten (13 per cent) were noted to have a hernia by the family doctor and were treated conservatively (five inguinal, four femoral, one incisional), nine (11 per cent) were noted to have a hernia during previous non-surgical hospital admissions and were treated conservatively (five inguinal, three femoral, one epigastric), while nine (11 per cent) had previously been assessed by surgeons with a view to hernia repair (three inguinal, three femoral, two paraumbilical, one incisional). Of the last nine patients, five were considered unfit for elective repair, three were on waiting lists for operation and one had refused surgery. Thirty-two patients (40 per cent) developed strangulation within 7 days of noticing the hernia (23 femoral, eight inguinal, two paraumbilical) One patient referred to above developed a strangulated left femoral hernia within 1 month of repair of the right side. The duration of hernia in one 90-year-old woman who presented with a strangulated obturator hernia was unknown.

Although femoral hernias (23) were more likely than inguinal (eight) to strangulate within 7 days of developing ($P < 0.01$), 14 femoral hernias had been present for at least 1 month before strangulation.

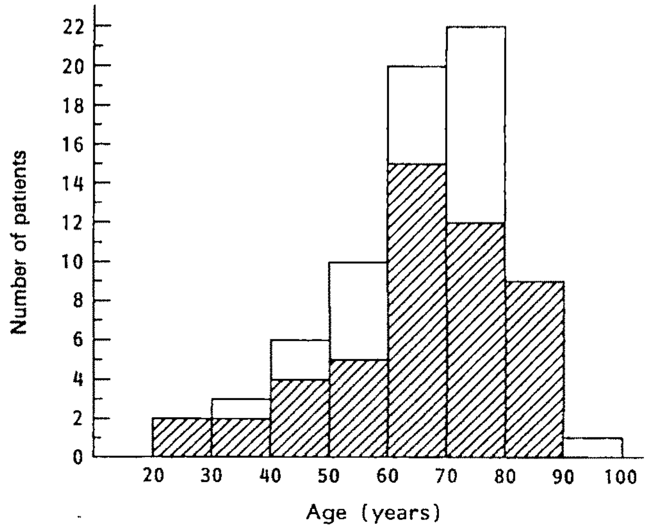

Figure 1 *Age and sex distribution of 79 patients with strangulated hernias* □, *females;* ■, *males*

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Table 1 *History of the presence of a hernia related to age*

Age (years)	Presence of hernia before strangulation*	
	<7 days	>30 days
90+	1	—
80–89	11	4
70–79	7	14
60–69	5	15
50–59	4	6
40–49	3	3
30–39	1	2
20–29	—	2
Total	32	46

* Duration of hernia in one patient was unknown

Table 2 *Operative risk factors in patients with noted hernia for at least 1 month before strangulation*

Age (years)	ASA grade		
	I	II	III
90+	—	—	—
80–89	1	0	3
70–79	2	0	6
60–69	4	1	7
50–59	2	—	1
40–49	1	—	—
30–39	—	—	—
20–29	—	—	—

ASA, American Society of Anesthesiologists

The general condition of the 28 patients whose hernia had been noted previously by medical personnel (family doctor, non-surgical hospital personnel or surgeons) but who had not been operated on is expressed using the American Society of Anesthesiologists (ASA) grading system[5] and is detailed in *Table 2*. Six otherwise healthy patients (ASA I: three inguinal, two femoral, one incisional), one patient with rheumatoid arthritis (ASA II) and 12 patients with other life-threatening conditions (ASA III: six inguinal, five femoral, one epigastric) had not been referred for surgical assessment. Of the nine patients who had been assessed surgically, one patient (ASA I) had refused surgery and five were considered unfit (two inguinal, two femoral, one paraumbilical), the reasons being poor general condition (ASA III) in four patients and gross obesity in one patient with a paraumbilical hernia Three patients had been on the waiting list for elective repair, one for 9 months and two for at least 2 years. The reason why the last two had not undergone repair is unclear. The underlying pathology in the 17 patients who were considered 'high risk' (ASA III) included, either alone or in combination, chronic obstructive airways disease (12), congestive cardiac failure (nine), hypertension (five), ischaemic heart disease (four) and cerebrovascular disease (three).

Bowel resection was required in 13 patients (ten femoral, three inguinal), eight of whom developed strangulation within days of the hernia appearing. Seven patients died during the same hospital admission (hospital mortality rate 9 per cent). The causes of death included bronchopneumonia (three), cerebrovascular accident (one), renal failure (one), metastatic carcinoma (one) and intra-abdominal sepsis in a 47-year-old patient who required bowel resection for a strangulated femoral hernia. Three of the deaths occurred in the group of 13 patients who required bowel resection. The median postoperative hospital stay was 9 days (range 4–56 days), with 33 patients in hospital for less than 7 days, 25 for 7–14 days and nine for 14 days or more. Duration of postoperative stay was unrecorded in five patients.

Discussion

Strangulated hernias in this and other recent series[2–4,6] are associated with a mortality rate of approximatly 10 per cent and a significant morbidity in terms of postoperative complications and duration of postoperative hospital stay[2–4]. Mortality and morbidity have been attributed not only to patient factors, such as bowel strangulation which requires resection[2,3] or coexistent medical illnesses[2], but also to poor operative technique and inadequate resuscitation of patients before surgery[7]. In contrast, mortality following elective repair, even in 'high-risk' patients, is now negligible[8] and postoperative stay is less than 5 days in the vast majority of cases[5,7], which is approximately half the mean postoperative stay of patients in this series. The cost effectiveness of a policy of prompt elective repair is immediately obvious and raises the question of why so many patients today still present with strangulation.

Only three patients (4 per cent) in this series strangulated while on the waiting list for elective repair, which would refute the suggestion by Allen *et al.* that many patients, particularly elderly patients, strangulate while languishing on operating waiting lists[3], and the study suggests that three other factors are primarily responsible. Firstly, a large proportion of hernias (40 per cent), particularly femoral, strangulated almost immediately, presumably before patient notification of the family doctor and certainly before elective repair could be carried out. Secondly, a significant percentage of patients (23 per cent) failed to notify their family doctor despite noting the hernia for at least 1 month, suggesting a lack of public awareness of the dangers of hernia strangulation. Thirdly, many patients (24 per cent) were known by medical personnel to have had a hernia but surgical assessment had not been arranged, suggesting a reluctance on behalf of non-surgical medical personnel to refer patients with known risk factors, factors which, if appropriately treated preoperatively, should no longer be considered contraindications to elective hernia repair, given the current status of local and regional anaesthesia[7].

This study supports the view that all patients with abdominal wall hernias should be offered surgery[3]. While accepting that an unavoidable number of patients will continue to present with strangulation immediately after their hernia develops, a policy of prompt patient notification of their family practitioner followed by prompt referral and elective repair will greatly reduce the current incidence of strangulated hernias in adults.

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Short notes

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Adult intussusception in Glasgow, UK

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The review of adult intussusception in the Greater Glasgow Health Board area[1,2] is extended to incorporate a further 33 cases occurring between 1974 and 1988.

Adult intussusception is an uncommon condition, between two and three new cases occurring in a population of approximately 1000 000 per annum. Previous studies from both sides of the Atlantic[3–10] have noted that, in contrast to childhood, the majority of cases are secondary to a causal lesion In Glasgow, two previous studies[1,2] covering the period from 1954 to 1974 suggest that there is a local propensity toward an idiopathic aetiology in up to 50 per cent of patients. Cases of retrograde jejunogastric intussusception following gastroenterostomy, and rectal prolapse were excluded from the study.

Patients

All patients discharged from the five Glasgow teaching hospitals with a diagnosis of intussusception were identified through the Scottish Home and Health Department's computerized Diagnostic Coding Index (560·0). Thirty-three patients were identified in the period from 1974 to 1988; each was studied to identify the site, the causal pathology, the presenting features, the accuracy of preoperative diagnosis, the method of diagnosis and the success of treatment.

Results

Age at presentation ranged from 18 to 83 years. Abdominal pain, usually colicy in nature, was universal. The other presenting symptoms of vomiting, distension, diarrhoea, constipiation or rectal bleeding were more variable and were dependent on the site of the lesion in the gastrointestinal tract. An abdominal mass was identified at presentation in 12 patients (36 per cent), although its significance was usually missed. Diagnosis was made at laparotomy in 30 patients (91 per cent) with a mean delay from admission to diagnosis of 3 days. The site of intussusception was as follows: one pyloroduodenal, eleven enteric, five ileocolic, seven caecocolic and nine colocolic.

One patient, who presented with gastric outlet obstruction, had a negative endoscopy and barium meal and was diagnosed at laparotomy to have a retrograde intussusception of the duodenal mucosa. In the small bowel, the majority of intussusceptions proved to be idiopathic (59 per cent); the others resulted from benign or malignant submucosal lesions. In the large bowel a malignant cause was found in ten patients (63 per cent), a benign cause in four (25 per cent) and an idiopathic aetiology was unusual.

Thirty-two patients underwent laparotomy. One elderly woman died shortly after admission, the diagnosis being made at post mortem. In cases of secondary intussusception the procedure performed was dictated by the causal pathology (*Table 1*). In idiopathic lesions there was variation in management: three patients required resection of ischaemic bowel; of the two idiopathic large bowel cases, one had a resection, the other a caecopexy (neither have recurred); in the small bowel intussusceptions, two patients underwent resection, the remaining five simply required reduction without fixation. There was no perioperative mortality. In a follow-up ranging from 1 to 14 years, none of the patients has developed a recurrent intussusception.

Discussion

A further 33 cases of adult intussusception are presented. Combining the three Glasgow studies, there are 83 patients who have presented over 34 years, with idiopathic aetiology occurring in 36 cases (43 per cent). However, 56 (67 per cent) cases involved the small bowel, which is a considerably higher proportion than in other series[3–10], and it would appear that it is the frequency of small bowel disease that distinguishes this population, rather than a local difference in aetiology. Of the 36 patients with idiopathic intussusception, 19 required resection for irreducibility or infarction; the remaining 17 had simple reduction without fixation. No patient has developed a recurrent intussusception.

In conclusion, therefore, we would suggest that:

1. Small bowel intussusceptions are more common in the west of Scotland than in other reported series
2. Idiopathic intussusceptions may be adequately treated by reduction alone, provided the bowel is viable
3. Preoperative diagnosis is rare and demands a high index of suspicion.

Table 1 *Causal pathology of the intussusception*

Pathology	No of patients
Small bowel	
Idiopathic	10
Lipoma	3
Melanoma	1
Lymphoma	1
Leiomyoma	1
Hamartoma	1
Total	17
Large bowel	
Idiopathic	2
Adenocarcinoma	9
Adenoma	3
Lymphosarcoma	1
Mucocele	1
Total	16

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Sister Mary Joseph's nodule: a study of the incidence of biopsied umbilical secondary tumours in a defined population

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Metastasis to the umbilical skin, first described by Storer[1] and often known as Sister Mary Joseph's nodule, is generally taken as a rare sign of extensive intra-abdominal tumour spread, indicating a very poor prognosis[2,3]. We have reviewed 33 cases diagnosed by biopsy in Northern Ireland, over 15 years. For the first time for this condition, we have related the total number of biopsies to a known, stable population and to reported mortality figures for various primary malignant tumours in that population.

Methods

The histopathology records of the Royal Victoria Hospital, Belfast and the Belfast City Hospital between 1970 and 1984 incorporate 89 per cent of all surgical specimens for Northern Ireland. The notes and slides of each identified case were reviewed. Death certificates were examined in the cases of patients who died outside hospital. The annual incidence of biopsied umbilical secondary tumours was calculated in relation to the average total population of Northern Ireland during the study period. The relative frequency of umbilical secondaries was then calculated in terms of the mortality rate associated with each of the corresponding primary tumours, as reported in the official death certification statistics of the Registrar General for Northern Ireland

Results

All 33 cases studied (19 female, 58 per cent; 14 male, 42 per cent) were adenocarcinomas. The mean age on diagnosis was 64 years. Patients survived for between 1 week and 67 months, the mean survival time being 8 months. The primary tumour site was not identified in seven cases (21 per cent). It is of interest that the mean survival in this group was much greater than for any of the identified primary tumours. The commonest identified primary was ovarian carcinoma (eight cases, 24 per cent), followed by carcinoma of colon and stomach (six cases each, 18 per cent). Pancreas (three cases, 9 per cent), lung (two cases, 6 per cent) and kidney (one case, 3 per cent) were the other identified primary sites. The mean population of Northern Ireland over the 15-year period was 1550 100. The incidence rate of biopsied umbilical metastasis was thus 0·142 per 100 000 population per year.

In ten cases (30 per cent) the umbilical secondary was the first sign of malignancy, while in two other cases (6 per cent), the metastasis heralded a decline due to dissemination of a previously diagnosed primary. Cutaneous secondaries are usually associated with a rapidly fatal course but six of our patients (18 per cent) survived longer than 1 year and one lived for over 5 years.

Table 1 relates registered deaths to biopsied umbilical metastases. One such lesion relates to 129 recorded deaths for ovarian carcinoma, making this the primary tumour most likely to give rise to the phenomenon. The corresponding figures for gastric and large bowel primaries are 1:765 and 1:1044 reported deaths, respectively. In men, these were the two commonest sites, accounting for 64 per cent of cases in male patients.

Discussion

In this series an ovarian primary was the commonest identified cause of a biopsied umbilical secondary. In two other large series, stomach, colon, ovary and pancreas were identified, in that order, as the main primary sites[4,5]. The relative frequency will reflect the referral and work patterns of the hospitals on which any study is based. Previous authors have been unable to relate this condition to a defined population; the residential stability and administrative isolation of Northern Ireland has provided us with such an opportunity.

Sources of error include a 10 per cent under-estimation of total cases, owing to incomplete coverage. In the calculation of relative frequencies, there is additional uncertainty associated with death certification data. Autopsies were not carried out in any of these cases. The use of mortality as denominator over-estimates the relative frequency of umbilical secondaries from the less aggressive primary tumours, such as large bowel, reflecting their favourable cure rates. The absence of an effective cancer registry in Northern Ireland means that the corresponding incidence data, which would have been preferable for this calculation, were not available.

In 12 of our 33 cases (36 per cent), the biopsy diagnosis was

Table 1 *The numbers of umbilical metastases originating at each primary tumour site, the mean survival time for each primary site, the numbers of recorded deaths due to tumours at this site and the estimated relative frequency of biopsied umbilical metastasis*

Primary site	No. of cases 1970–84	Male	Female	Mean survival (months)	No of deaths 1970–84	Relative frequency of biopsied umbilical metastasis
Ovary	8	–	8	8	1036	1:129
Colon	6	5	1	4	6265	1:1044
Stomach	6	4	2	3·5	4590	1·765
Pancreas	3	2	1	1·7	2270	1.757
Lung	2	1	1	3·0	8937	1:4468
Kidney	1	1	0	13 days	599	1:559
Unknown	7	1	6	21	—	—
Total	33	14	19			

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of practical clinical significance. In the other 21 cases, the biopsy was either an incidental, cosmetic or palliative procedure. Wide variations in these categories can be expected in different populations, reflecting different surgical traditions and changing patterns of diagnosis and treatment. In many other cases, no doubt, the phenomenon was noted clinically but did not call for biopsy.

In conclusion, ovarian carcinoma was the commonest cause of Sister Mary Joseph's nodule, both in numbers and relative frequency. In men, carcinoma of stomach and colon predominated. This is a more common phenomenon than is generally appreciated and it is not invariably associated with a terminal illness.

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Phenol treatment of pilonidal sinuses of the natal cleft

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Pilonidal disease of the natal cleft is a common condition responsible for much morbidity, and its treatment places a burden on hospital and community resources. Many methods of treating chronic pilonidal sinuses have been described and the optimum treatment remains a topic for debate. Phenol injection of pilonidal sinuses has been the routine practice of two consultant surgeons in Ipswich for over 15 years, while the remaining consultant surgeons excise and pack sinuses. The relative merits of these procedures, as used in 169 patients over a 15-year period, have been reviewed.

Patients and methods

The hospital records of patients presenting with acute or chronic pilonidal disease, between 1970 and 1985, were reviewed. Age, sex, presentation, number of sinus openings, treatment, complications, inpatient stay, and outcome were recorded.

During the period studied 226 patients were treated for natal cleft pilonidal disease. Seventy-four patients (49 male patients and 25 female patients) presented as emergencies with pilonidal abscess and 152 (114 male patients and 38 female patients) were referred with a chronic pilonidal sinus. Mean age at presentation was 26·6 years (range 14–62 years). Twenty-eight patients presenting with an abscess subsequently developed a chronic sinus, resulting in 180 patients seen for pilonidal sinus. Eleven received no treatment, 65 were treated by excision and packing and 104 received phenol injections.

Excision of sinuses was performed *en bloc* and the wounds were packed and allowed to heal by secondary intention. The technique of phenol injection was similar to that described by Maurice and Greenwood[1]. Under general anaesthesia, with an endotracheal tube, the patient was positioned prone and the buttocks liberally covered with paraffin jelly. Eighty per cent phenol was injected into the sinus, left for 1 min, and the sinus then curretted; this was repeated three times. Patients with asymptomatic, shallow sinuses were advised that treatment was unnecessary.

Following excision of sinuses, patients received daily dressings until discomfort subsided sufficiently to allow a district nurse to continue the dressings at home. Thereafter patients were reviewed at 2–3 week intervals until their wound healed. Patients treated by phenol injection were kept in hospital overnight, and allowed home the following day with instructions to bathe daily and keep the area shaved. Regular dressings and analgesia were not required by patients treated with phenol. Outpatients review was continued at 2–3-week intervals until the sinus healed. Fifty-two (80 per cent) patients treated by excision and 79 (76 per cent) of those treated with phenol were seen 3–6 months after healing to exclude or identify recurrence.

Results

An initial cure rate of 83 per cent was obtained following excision compared with 65·4 per cent following phenol injection. Second treatments using the same methods on individual patients improved these figures to 86 per cent for excision and 75 per cent for injection. Information on the number of sinus openings was available for 42 patients treated by excision and 65 patients treated by injection. Analysis of cure rate relative to number of sinus openings showed that for sinuses with one or two openings there was no significant difference between excision and injection.

Comparison of inpatient stay and time to healing revealed a significantly earlier discharge from hospital and shorter time to healing following phenol injection (*Table 1*) During a mean follow-up of 8 months (range from 3 months to 4 years) recurrent sinuses after initial healing occurred in ten patients treated by excision and 12 treated by injection.

Following 130 phenol injections in 104 patients sterile abscesses developed in seven and cellulitis in one patient. There was no relationship between number of sinus openings and development of an abscess. The abscesses and related sinuses were all cured by surgical drainage and the cellulitis settled with antibiotic treatment. No other complications were seen in either treatment group.

Discussion

Pilonidal sinus of the natal cleft can be a chronic, recurring condition which is difficult to cure. Many treatments have been proposed but few provided long-term good results. The traditional methods of *en bloc* excision and laying open of sinuses result in hospital admissions of 5–29 days, healing times of 6–10 weeks and recurrence rates of 8–21 per cent[2–5], similar to the findings in this series. Previous attempts to improve on these results by various methods of primary closure reduced the healing times to under 2 weeks, but hospitalization remained similar at 9–18 days and recurrence rates varied between an encouraging 2–4 per cent[6–8] and a disappointing 8–40 per cent[2–4,9,10]. The Millar–Lord technique[11] produces a healing time of 7 weeks and a recurrence rate of 23 per cent[12], similar to results following phenol injection.

There have been four small series reporting phenol injection of pilonidal sinuses and these describe hospitalization of 2–3 days, healing within 3–6 weeks, return to work in 1–2 weeks and recurrence rates of 9–27 per cent[1,13–15]. This report confirms the brief inpatient stay, the reduced time to healing and a recurrence rate similar to that following excision and packing. The 5·4 per cent incidence of sterile absence following

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Table 1 *Duration of inpatient stay and time to healing*

		Time to healing	
Method of treatment	Inpatient stay (days)	All sinuses (weeks)	1–2 openings (weeks)
Excision and packing	10·4±6·2 (3–30)	13·0±7·5 (2–37)	10·2±6·3 (3–23)
Unpaired *t* test	*P*<0·0001	*P*<0·001	*P*<0·001
Phenol injection	1·8±0·8 (1–5)	8·7±5·5 (1–23)	5·9±2·4 (2–12)

Results are given as mean ±s.d. with ranges in parentheses

injection is disappointing, but might be reduced by more gentle injection of the phenol.

This study shows that for pilonidal sinuses of the natal cleft, with one or two openings, phenol injection is an effective treatment. The method produces results which are similar to those achieved by surgical excision but has the advantages of a reduced requirement for anagelsia and dressings, and a shorter inpatient stay and time to healing. We advocate phenol injection as the first line of treatment for uncomplicated pilonidal sinuses of the natal cleft but consider excision more suitable for complicated sinuses with three or more openings. The lack of long-term follow-up for both groups does not deter us from making this recommendation; late recurrence is recognized after all forms of treatment and the advantages of phenol injection, outlined above, encourage us to recommend treating any recurrence with a second application of phenol before resorting to more aggressive methods.

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Serum phospholipase A_2 activity in acute pancreatitis: an early guide to severity

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Daily measurements of serum phospholipase A_2 activity were carried out on 73 consecutive patients admitted to hospital with acute pancreatitis. During the first 6 days there were significant differences in activity in those patients predicted as severe by multiple prognostic criteria when compared with those with mild disease. Follow-up studies at 6 weeks showed no difference between those graded as mild and those graded as severe at the time of attack. In the patients with elevated activity, nine had this at the time of admission and all were raised within 24 h. Elevated activity correlated well with the clinical outcome and showed good agreement with the multiple prognostic criteria in the prediction of severe disease. It is suggested that measurement of serum phospholipase A_2 activity may provide a simple test for the early identification of most patients with severe acute pancreatitis.

Keywords: Phospholipase A_2, acute pancreatitis

The use of multiple laboratory criteria[1,2] is a well established and widely used method for predicting severity in attacks of acute pancreatitis. In the early stages of the disease this system offers a significant improvement over clinical judgement for identifying severe attacks, but it can take up to 48 h to complete the assessment, by which time the advantage is lost[3]. A more rapid answer can be obtained by using the technique of diagnostic peritoneal lavage, but clinical reluctance and patient refusal have limited its application[4]. In recent years the measurement of serum phospholipase A_2 activity has been reported as providing a simple and rapid alternative for differentiating mild from severe disease. Studies from Finland[5,6] and Germany[7] have shown that in haemorrhagic pancreatitis the enzyme activity is significantly elevated early in the disease, whereas in oedematous pancreatitis only modest elevations occur. The question remains about how the measurement of phospholipase A_2 activity can help in discriminating mild from severe disease. This paper reports a prospective study measuring serum phospholipase A_2 activity during 73 attacks of acute pancreatitis. The results were compared with the multiple prognostic criteria for their accuracy in predicting severe acute pancreatitis.

Patients and methods

The study group comprised 73 consecutive patients admitted to the Royal Hallamshire Hospital with acute pancreatitis between December 1984 and February 1987. The diagnosis of acute pancreatitis was made on the finding of a serum amylase level >1000 units/l (Phadebas method, Pharmacia G.B. Ltd., Milton Keynes, UK) and a consistent clinical picture of abdominal pain. All patients were seen on admission by one of the authors (A. J. G.) and a full drug and alcohol history was taken. Blood samples were obtained for severity grading by the multiple prognostic criteria[2] and phospholipase A_2 analyses. Blood samples were taken for phospholipase A_2 analysis on admission and then daily for a period of up to 8 days. An additional sample was taken at the out-patient appointment 6 weeks after discharge from hospital.

All patients were initially treated under conservative management. This consisted of correction of fluid and electrolyte imbalance, nasogastric aspiration, and analgesia with opiates; antibiotics were not routinely given.

The biochemical and haematological tests for diagnosis and severity prediction were performed in the routine hospital laboratories. The phospholipase A_2 activity determinations were carried out using the method developed in our department[8]. Briefly, this involves quantifying the palmitic acid released as a result of the enzyme action on dipalmitoyl phosphatidylcholine, by capillary gas–liquid chromatography. The results are expressed in units per litre of serum.

Results

The aetiological association of the 73 attacks of acute pancreatitis are shown in *Table 1*. There was an equal number of men and women with a mean age of 59 years (range 23–85 years). The clinical outcome classified 22 patients as severe, with eight fatal attacks, four patients who developed pancreatic pseudocysts (>2 cm diameter), and ten patients who required a hospital admission, as a result of acute pancreatitis, of >14 days.

The phospholipase activities are shown in *Table 2*. Statistical analysis, using the Mann–Whitney *U* test, shows that there are significant differences during the first 6 days between attacks graded by prognostic indices, as mild and attacks graded as severe, but this disappears by the time of follow-up at 6 weeks (*Figure 1*).

In an attempt to define a level of phospholipase activity that would separate clinically mild from clinically severe disease, the data were reviewed retrospectively. The highest value from each clinically mild patient was taken and the mean and standard deviation were calculated. Two standard deviations above this mean value of 45 units/l gave a cut-off value of 85 units/l, above which the patients were graded as phospholipase A_2 severe. Of the 73 patients in the study, 11 showed values >85 units/l, of whom eight had been predicted as having severe disease by multiple prognostic criteria. There was no relationship between the aetiological factors and raised phospholipase activity, the aetiologies merely reflecting the group as a whole. The interesting finding was that nine of the phospholipase A_2 severe patients had raised activity on admission to hospital and all were elevated within 24 h.

Table 1 *Aetiological factors associated with 73 attacks of acute pancreatitis*

Aetiology	Total	Percentage
Gallstones	45	62
Alcohol	18	25
Idiopathic	3	4
Post-ERCP	2	10
Steroids	1	
Alcohol and gallstones	1	
Postoperative	1	
Hypothermia	1	
Hyperlipidaemia	1	

ERCP, endoscopic retrograde cholangiopancreatography

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Table 2 *Phospholipase activity results and statistics graded by multiple prognostic criteria*

	Mild			Severe		
Day	Number of points	Mean (units/l)	s.e.m.	Number of points	Mean (units/l)	s.e.m.
0	57	29·4	3·2	16	76·1	13·8
1	57	29·0	4·6	16	85·4	20·3
2	57	32·2	6·2	14	111·1	31·2
3	53	22·2	2·4	13	96·4	32·3
4	50	19·7	2·4	11	72·9	28·3
5	40	20·9	3·3	10	77·2	24·7
6	29	20·8	3·5	8	43·2	10·2
7	22	26·4	6·2	7	52·6	16·9
8	17	23·0	5·5	7	40·3	15·4
Follow-up	35	6·0	1·1	4	6·5	1·6

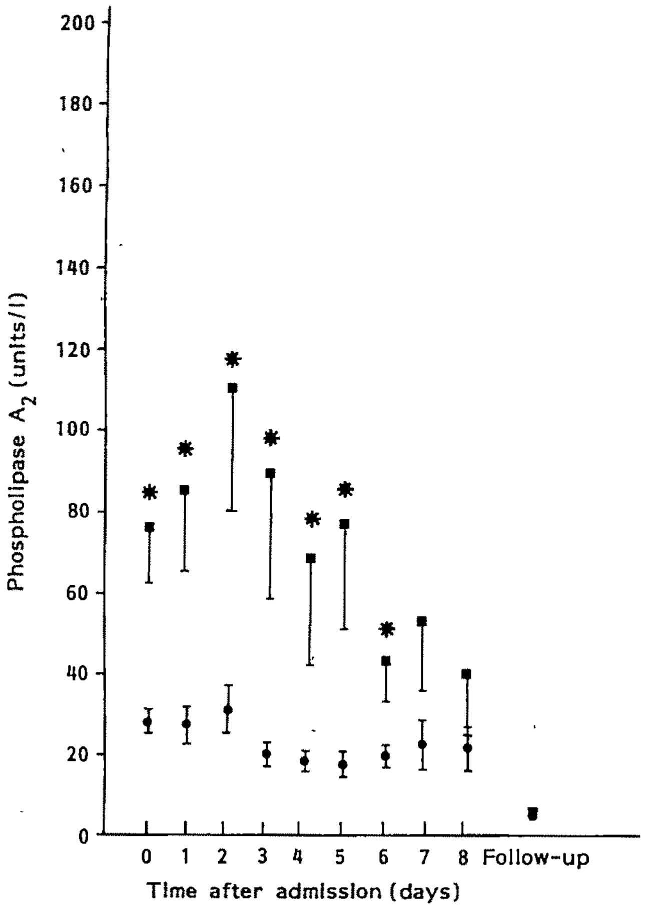

Figure 1 *Phospholipase A_2 activity (mean+s.e.m.) in 73 patients admitted with acute pancreatitis. Attacks graded as severe (■) or mild (●) by multiple prognostic criteria (n=16) showed significantly increased activity over mild attacks for days 0–6* * P<0·03

Discussion

The success of the multiple prognostic criteria in predicting severe disease was similar in this study to those of previous reports[4,9]. Of the 16 patients with predicted severe attacks, eight died and, of the survivors, three were discharged from hospital within 14 days, giving a true positive prediction of 81 per cent. In the 57 patients predicted as mild, four of them developed pancreatic pseudocysts and four required a hospital stay >14 days, giving an accuracy of 86 per cent.

When phospholipase A_2 activity was used to assess severity the success for the severe cases was similar to that of the multiple prognostic criteria (χ^2 test with Yates' correction, $P<0·001$).

Ten of the 11 patients with raised activity had clinically severe disease (91 per cent true positive). However, the success for mild attacks was not so good and it is important to note that three deaths occurred in patients in whom no marked rise in activity was seen. One patient was an early death within 24 h from bilateral adrenal haemorrhage, and the other two were late deaths at 31 and 90 days respectively. Despite the fact that one of these late deaths was not pancreatitis related, all three had been predicted as severe attacks by multiple prognostic criteria. In the remaining 59 phospholipase A_2 mild cases there were four pancreatic pseudocysts recorded and four patients whose hospital stay was greater than 14 days, giving an accuracy of 82 per cent.

Although none of the tests used in the multiple prognostic criteria method for predicting severity of attack is specific for acute pancreatitis, the tests do, in combination, provide a reliable means of identifying patients with severe disease. This study has shown that the estimation of serum phospholiphase A_2 activity may provide a more rapid prediction of severity, elevated levels showing a good correlation with severe disease. The recent publication of methods[9,10] suitable for routine use should allow more widespread application of this technique.

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APACHE II score in massive upper gastrointestinal haemorrhage from peptic ulcer: prognostic value and potential clinical applications

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This study examined the prognostic value of the APACHE II scoring system in patients undergoing emergency operations for bleeding peptic ulcer. There were 96 operations for gastric ulcers and 58 for duodenal ulcers. The mean scores in survivors and in patients who died were 10·8 and 17·5 respectively. None of the 66 patients with an APACHE II score <11 died, while the mortality rate in those scored >10 was 22 per cent. In patients scored >10 non-resective procedures carried less risk of mortality than gastectomy. The APACHE II score is useful when measuring the severity of the acute disease and predicting the outcome in these patients. If used in daily practice it may assist the surgeon in stratifying patients into a low-risk group (score <11) in which major operations are well tolerated and outcome is favourable and a high-risk group (score >10) in which the risk of mortality is high and the performance of procedures of lesser magnitude is probably more likely to improve survival.

Keywords: APACHE II, outcome prediction, upper gastrointestinal haemorrhage, emergency gastroduodenal operations

The procedure of choice for the surgical control of a bleeding peptic ulcer is controversial. While some authors[1,2] advocate the use of truncal vagotomy and antrectomy (TV+A) for a bleeding duodenal ulcer, others[3] claim that truncal vagotomy and a drainage procedure (TV+D) is safer. The same argument involves the management of bleeding gastric ulcers. Whilst partial gastrectomy continues to be the procedure of choice in many major centres[1,2,4], others attribute lower mortality rates to more conservative operations such as TV+D[5] or simple undersewing of the ulcer alone[6].

The comparison of results is distorted by the fact that sicker patients are usually selected for the more conservative operations. Thus, for example, McGuire and Horsley[7], operating on bleeding duodenal ulcers, cited a mortality rate of 21 per cent for TV+A and 45 per cent for TV+D. It is widely recognized that elderly patients, especially those with associated medical disease, represent a 'high-risk' group that tolerates poorly the combined acute insult of bleeding and the subsequent operative procedure[3,8,9]. However, there is general lack of agreement about the definition of the 'high-risk' patient. Yajko *et al*[4] advocated TV+A for their 'good-risk' patients with bleeding duodenal ulcers; TV+D was reserved for the 'high-risk' group. The selection criteria for either group were not defined and were probably left to the clinical judgement of the individual surgeon. Likewise, Herrington and Davidson[1] would reserve TV+D for the 'extremely high risk patient who it is felt will not tolerate the more lengthy procedure' of TV+A for duodenal ulcers, and partial gastrectomy for gastric ulcers. Welch *et al.*[2] in a large retrospective study attempted to subdivide their patients into four risk-grade groups. Mortality rates were similar for TV+D or TV+A in all age and risk groups; precise definition of the various risk grades is not given. Rogers *et al.*[6] studied the surgical management of bleeding gastric ulcer patients in whom the mortality rate for partial gastrectomy was 26 per cent and for undersewing alone was 10 per cent. No evidence to support the similarity of their patients in terms of surgical risk is presented.

Five main factors determine the outcome of an acute disease: the patient's age, the prior health status of the patient, the severity of the disease, the type of the disease, and the treatment given. The APACHE II scoring system[10] has gained recent popularity in the measurement of severity of acute illness It takes into account the first three factors. Obviously, if the influence of any given therapy is to be assessed, the score should be determined before treatment is commenced. The predictive power of APACHE II has been validated in many acutely ill patients admitted to intensive care units with common medical and surgical diseases[10]. Others have found APACHE II to be useful in predicting outcome in intra-abdominal infections[11–13] and acute pancreatitis[14].

The reasons for this study are threefold: firstly, to attempt to validate the prognostic value of APACHE II in patients undergoing emergency operations for the control of bleeding peptic ulcers; secondly, to assess its usefulness as a potential clinical research tool; and, thirdly, to use this method for the stratification of patients according to their surgical risk to assist in making rational and objective treatment decisions

Patients and methods

All patients with upper gastrointestinal haemorrhage admitted to the J. G. Strijdom Hospital, Johannesburg are cared for by one surgical unit The 'on duty' surgical team assumes responsibility for resuscitation, endoscopy, surgery (if indicated) and future care of these patients

The decision to perform an emergency operation is taken by the consultant surgeon on duty, based on clinical and haematological evidence of persisting or recurrent bleeding The choice of procedure performed is left to the surgeon and no strict protocol has been laid down However, during the study period, the general trend was to perform partial gastrectomy for bleeding gastric ulcers and TV+D for duodenal ulcers.

All patients who underwent emergency surgery for bleeding peptic ulceration between 1980 and 1987 inclusive were identified from their discharge books and their summaries were retrieved Patients who

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underwent semi-urgent operations (i.e. elective procedures performed on the same hospital admission) were excluded.

APACHE II score was calculated according to the method of Knaus *et al.*[10]. For each physiological variable we included the most abnormal measurement of that variable within the 24 h before operation. In the situation in which a variable had not been measured in the 24 h before surgery, the last measurement of that variable before treatment was used If a particular variable was never measured, it was considered normal and a 0 score was entered. Similarly, applied retrospective APACHE II scoring was validated in patients with abdominal sepsis[11]. Any death during the first 30 postoperative days was considered an operative mortality.

Results

In the 8-year study period, 900 patients with upper gastrointestinal haemorrhage were admitted to our unit; a total of 154 patients underwent emergency surgery for bleeding gastric ($n = 96$) or duodenal ($n = 58$) ulcers. Clinical details of patients in both ulcer groups and their APACHE II scores are represented in *Table 1*.

Nineteen patients died (12·3 per cent). The mean age of the patients who died and those who survived was 71·7 and 58 years respectively. Twelve deaths were due to 'medical' causes such as respiratory, cardiac, renal or hepatic failure. Two patients had cardiac arrest in the perioperative period: one of them shortly after partial gastrectomy for bleeding gastric ulcer; the other, operated on for bleeding duodenal ulcer, shortly after induction of anaesthesia. Five deaths were due to 'surgical' causes: in three patients due to massive rebleeding following partial gastrectomy, and in two due to anastomotic leaks after partial gastrectomy and TV + D.

Table 1 *Patient details and mean APACHE II scores*

	Gastric ulcer	Duodenal ulcer
No. of patients	96	58
Male:female	59:37	41:17
Mean age (years)	59·6	61·2
Mean APACHE II score	12	10·9
Mortality rate (%)	12 (13)	7 (12)
Mean APACHE II score of survivors	11·4	9 8
Mean APACHE II score of patients who died	16·2	19·4

Overall, the mean APACHE II score in the 154 patients was 11·6 (range 2–25). The mean APACHE II score in patients who died was 17·5 compared with 10·8 in survivors.

An increasing APACHE II score was associated with an increased likelihood of mortality for patients with both gastric and duodenal ulcer (*Table 2*). Interestingly, none of the 66 patients with APACHE II score < 11 died, while the mortality in those > 10 was 22 per cent.

Table 3 demonstrates the mean APACHE II score and the mortality rates in patients undergoing different procedures. Patients in the gastric ulcer group, subjected to non-resective operations (undersewing or TV + D), had higher scores than those undergoing partial gastrectomy. This can obviously be attributed to selection of the lesser procedure for the clinically high-risk patient. That was not the case in the duodenal ulcer group where patients receiving TV + A and TV + D had almost similar scores.

Tables 4 and *5* examine the mortality rates for the different procedures performed in subgroups of patients with different APACHE II scores.

Table 6 shows the mortality rates of the various procedures in patients with scores > 10. Limited operations, such as undersewing or TV + D in the case of gastric ulcer and TV + D in duodenal ulcer, carried less risk of mortality than resective operations (partial gastrectomy or TV + A) in this high-risk group. These results, however, did not reach statistical significance.

Discussion

As pointed out above, the literature that deals with the management of massive upper gastrointestinal haemorrhage lacks precision and uniformity in its definition of the severity of illness of the patients studied and their operative risk. A better method is needed in the emergency preoperative evaluation of these patients. In this study we have attempted to find out whether the APACHE II system could achieve such a goal. Our results validate the prognostic value of the APACHE II scoring system in patients who undergo operations for upper gastrointestinal haemorrhage. It demonstrates that the increased surgical risk of the individual patient is reflected by the APACHE II score, which in turn correlates well with the probability of dying. Of course, a search for factors that influence mortality in patients with upper gastrointestinal bleeding has been attempted in the past[3,9]. The APACHE II

Table 2 *Mortality according to the APACHE II score*

	Scores									
	0–5		6–10		11–15		16–20		21–25	
	No. of patients	No. of deaths	No. of patients	No. of deaths	No. of patients	No. of deaths	No. of patients	No. of deaths	No of patients	No. of deaths
Gastric ulcer	10	0	26	0	38	2 (5)	18	8 (44)	4	2 (50)
Duodenal ulcer	10	0	20	0	17	1 (6)	9	4 (44)	2	2 (100)
Total	20	0	46	0	55	3 (6)	27	12 (44)	6	4 (67)

Values in parentheses are percentages

Table 3 *APACHE II scores and mortality for different procedures*

	Gastric ulcer			Duodenal ulcer	
	Partial gastrectomy	Simple undersewing	TV + D	TV + A	TV + D
No. of patients	84	7	5	17	40
Mean score	11·4	17·5	14·4	11·4	10·6
No. of deaths	11 (13)	0	1 (20)	3 (18)	3 (8)

Values in parentheses are percentages. TV + D, truncal vagotomy and drainage procedure; TV + A, truncal vagotomy and antrectomy

Table 4 *Mortality in subgroups of patients with bleeding gastric ulcer*

	Partial gastrectomy		Simple oversewing		TV+D	
APACHE II score group	No. of patients	No. of deaths	No. of patients	No. of deaths	No. of patients	No of deaths
0–10	35	0	—	0	1	0
11–20	47	9 (19)	5	0	4	1 (25)
21–30	2	2 (100)	2	0	0	0

Values in parentheses are percentages. TV+D, truncal vagotomy and drainage procedure

Table 5 *Mortality in subgroups of patients with bleeding duodenal ulcer*

	TV+A		TV+D	
APACHE II score group	No. of patients	No. of deaths	No. of patients	No of deaths
0–10	8	0	22	0
11–20	8	2 (25)	18	3 (17)
21–30	1	1 (100)	0	0

Values in parentheses are percentages TV+A, truncal vagotomy and antrectomy; TV+D, truncal vagotomy and drainage procedure

Table 6 *Mortality according to procedure in patients with APACHE II score >10*

	No. of patients	No. of deaths
Gastric ulcer		
Partial gastrectomy	49	11 (22)
Simple oversewing/TV+D	11	1 (9)
Duodenal ulcer		
TV+A	9	3 (33)
TV+D	18	3 (17)

Values in parentheses are percentages TV+A, truncal vagotomy and antrectomy; TV+D, truncal vagotomy and drainage procedure

scoring system offers certain attractive advantages: its predictive power has been previously validated in a large number of critically ill patients admitted to intensive care units[10,15], in intra-abdominal infections[11–13], acute pancreatitis[14] and multiple trauma[16]. It measures the severity of the acute illness of the patient based on basic clinical examination (temperature, blood pressure, cardiac and respiratory rates and the level of consciousness) and a few simple laboratory investigations (red and white cell counts, serum sodium, potassium and creatinine levels, and arterial blood gas). In addition, it takes into account the patient's age and previous chronic health status, which in turn reflect their physiological reserve and their capability to withstand the combined insult of the acute disease and its surgical treatment. Consequently, a brief history and clinical examination combined with the above-mentioned laboratory variables should allow complete APACHE II scoring and precise stratification of patients to the various risk groups before operation in under half an hour.

All surgeons know that fit patients in good shape tolerate the operations well while the elderly and sick tend to fare badly. The mere fact that patients with low APACHE II scores survive and those with high scores die is therefore not a strong enough reason for surgeons to measure prognostic scores in their acute patients. What, then, are the practical applications of APACHE II scoring?

In this study, we divided our patient population into three prognostic subgroups. The first consists of patients with APACHE II score <11. Those in this group did well irrespective of the procedure selected; their youth and the relatively mild physiological compromise imposed by the haemorrhage on previously healthy organ systems allowed them to withstand any operative stress. The second group of patients with scores ranging between 11 and 20 represented a higher risk group with a higher mortality rate. The final group, with scores >20, consisted of severely compromised individuals who tolerated poorly any operation and hence had a high probability of dying. Similar patterns after division into three groups according to the APACHE II score were demonstrated in patients with abdominal infections[11,13].

Although the original APACHE II system was not developed as a basis for treatment in the individual patient, data from carefully described groups of patients can be used cautiously in decision making[17]. The knowledge that none of the patients in the present study with scores <11 died may suggest that operations of any extent would be relatively safe in such a subgroup. In this situation the objective scoring system should function as an aid to the well developed but subjective clinical judgement of the surgeon. The second and third groups represent severely compromised patients. Certainly, those with extremely high scores belonging to the third group would die despite maximal supportive therapy, and irrespective of the procedure chosen. It seems that in the majority of patients with APACHE II scores >10 the correct selection of the extent of the procedure may be important. Our study 'suffers' from paucity of high-scoring patients subjected to TV+A for bleeding duodenal ulcers or TV+D and/or undersewing alone for gastric ulcers. Our data imply, however, that in the high-risk patients, with scores >10, performing the lesser procedure may improve hospital survival.

Only one end-point, namely the death or survival of the patient, was used. Criteria such as the period of hospital stay or admission to an intensive care unit were not used; these may be influenced by the availability of facilities and differences in management policies between individual centres and clinicians.

Although there were no deaths among patients with scores <11 in this series, individuals with low scores do occasionally die. During the last 2 years we have prospectively measured the preoperative APACHE II scores in patients with intra-abdominal infections (M. Schein and G Gecelter, unpublished data). In over 100 patients studied to date we encountered two fatalities in those belonging to the low-risk group (<11), both dying after massive aspiration of gastric contents. Fatalities in the low-score group should be considered as 'unexpected', and are due to shortcomings in patient management.

The APACHE II score in its present form has a few noticeable weak points. For example, it does not take into account acute ischaemic electrocardiographic changes, the presence of severe arrhythmias or the history of a recent myocardial infarction – conditions which, if present, will add to the operative risk. A new version of the present score, the APACHE III, is in evolution in order to deal with these few deficiencies (W. A. Knaus, personal communication).

We conclude that the APACHE II score is useful in measuring the severity of acute disease and predicting the outcome in patients operated on for upper gastrointestinal haemorrhage. If used in daily practice as an objective aid to clinical judgement it may assist the surgeon in stratifying patients into a low-risk group in which major operations are well tolerated and outcome is favourable, and a high-risk group in which the probability of mortality is high and the performance of procedures of lesser magnitude is probably more likely to improve survival. Uniform scoring of the patients in these trials using a common language such as the APACHE II would improve patient stratification to the good-risk and poor-risk groups, enabling studies to be performed which would confirm or reject the suggestion that tailoring of the procedure to the patient's score would ultimately lead to improved survival.

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Short note

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Sigmoid volvulus in rural Ghana

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There is a marked geographical variation in the incidence of volvulus of the sigmoid colon. Holy Family Hospital, Berekum, Ghana lies in an area where sigmoid volvulus is especially common, and a detailed study covering the years 1975–82 was reported from Berekum by Schagen van Leeuwen[1].

This report records the experience with sigmoid volvulus over the following 5 years, from 1983 to 1987.

Patients and methods

The operative records of all patients treated for mechanical bowel obstruction at Holy Family Hospital, Berekum, between 1 January 1983 and 31 December 1987 were examined, as were the full medical records of all those patients treated for sigmoid volvulus. This 162-bed district hospital in the Brong Ahafo region of Ghana serves a population of 165 000 (1984 census)

Results

A total of 330 patients were treated for mechanical bowel obstruction during the period studied, of whom 73 (22 per cent) had volvulus of the sigmoid colon. The mean age of these 73 patients was 50·9 years, with the youngest aged 3 years and the oldest in his nineties. The male:female ratio was approximately 2:1 (48:25).

There were 12 deaths in the group, giving an overall mortality rate of 16 per cent. The main therapeutic procedure performed in each case and the associated mortality rate are shown in *Table 1*. The mortality rate was higher in female patients (24 per cent) than in male patients (12 per cent).

Table 1 *Main therapeutic procedure performed in 73 patients with sigmoid volvulus, and the associated mortality rate*

Procedure	No. of patients	No of deaths	Mortality rate (%)
Sigmoidoscopy and flatus tube insertion	15	2	13
Laparotomy and detorsion without subsequent resection	15	4	27
Elective sigmoid resection	35*	4	11
Emergency sigmoid resection	8	2†	25
Total	73	12	16

* Of the 35 patients in this group, 25 had had previous sigmoidoscopic insertion of a flatus tube and nine had had a previous laparotomy and untwisting of sigmoid volvulus. †One of these patients had survived an emergency Hartmann's procedure but died following an anastomotic leak after reanastomosis some months later

Discussion

Sigmoid volvulus is a dangerous condition with a significant risk of mortality. The principles of treatment are well established. Most patients can be successfully managed by Bruusgaard's method of sigmoidoscopy and the passage of a flatus tube[2] followed by elective sigmoid resection. A few patients need laparotomy to untwist the bowel, and occasionally emergency resection is required when non-viable bowel is present, when Hartmann's operation is the procedure of choice[1,3–5].

The number of cases of sigmoid volvulus presenting to Holy Family Hospital has fallen from an average of 18 per year (1975–82)[1] to 15 per year (1983–87). Coupled with the increase in population this probably represents a real decline in the incidence of the disease in the Berekum Jaman district.

The mortality rate has increased from 10 per cent in 1975–82 to 16 per cent in 1983–87. The reasons for this are not clear. The mean age of the patients was similar (48·7 and 50·9 years respectively), but there were relatively more female patients in the present study, in whom we noted a higher mortality rate. The results still compare favourably with those obtained in many western series[5,6].

There was a high mortality rate in those who rewquired emergency laparotomy. Of the 32 patients in this group, eight required emergency resection for non-viable bowel (25 per cent mortality rate). The other 24 patients had untwisting and deflation of the volvulus, with insertion of a flatus tube per rectum. Of these patients, nine subsequently underwent successful elective resection, but four of the other 15 died. Therefore the overall mortality rate in the 'laparotomy and untwisting' group was 17 per cent, which we consider to be high especially in view of the fact that 11 (46 per cent) of them went home without definitive treatment and therefore with a high risk of recurrence[7]. Shepherd[8] had similar results, with eight deaths in 49 patients (16 per cent mortality rate) treated by laparotomy and untwisting.

We confirm from this study that, for all its apparent simplicity, laparotomy and detorsion of sigmoid volvulus with viable bowel carries a significant mortality, and that it may not be the procedure of choice in those patients in whom sigmoidoscopic intubation has failed to deflate the bowel. Anderson and Lee[5] came to the same conclusion but the best procedure in this situation remains controversial (Hartmann's procedure, or resection and anastomosis with or without a 'protective' transverse colostomy).

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Conservative proctocolectomy: a dubious option in ulcerative colitis

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Conservative proctocolectomy was performed for ulcerative colitis in 19 patients, Crohn's disease in three and familial adenomatous polyposis in one. Healing was uncomplicated in only three patients (13 per cent). Eleven developed an anal discharge and nine an infected pelvic haematoma despite peranal drainage. Fourteen patients developed pelvic sepsis and, despite surgical curettage in 11, none healed. Six of these patients have had the anal sphincter divided, with healing in only one, and the anal canal has been excised in two. Eleven patients have ultimately healed at a median time of 28 months and eight have persistent sepsis after a median period of 45 months. Two patients with sepsis have had a successful ileoanal anastomosis. Conservative proctocolectomy cannot be recommended as a definitive operation for ulcerative colitis even though it may permit a subsequent restorative procedure.

Keywords: Ulcerative colitis, proctocolectomy

The 'conventional' operation for ulcerative colitis is a total proctocolectomy with an incontinent ileostomy[1]. Over the last 10 years, restorative proctocolectomy with removal of the colon, rectum and upper anal canal mucosa, and anastomosis of an ileal pouch to the anus, has become increasingly popular[2].

A modified technique[3] for total proctocolectomy, removing the colon and rectum whilst conserving the anus, was described in 1953. The aim of this operation was to avoid the perineal dissection which was often associated with considerable hypotension Colorectectomy and conservation of the anus was recommended more recently for inflammatory bowel disease[4] because it avoided a perineal wound and in women preserved the perineum for vaginal support.

This operation, alternatively called a 'conservative proctocolectomy', removes the entire colon and rectum and the mucosa from the upper anal canal but preserves the mucosa of the lower anal canal and the internal and external sphincters. Conservative proctocolectomy may be indicated in patients with ulcerative colitis when Crohn's disease cannot be excluded or when there is a coexistent adenocarcinoma. It may also be an option in patients who decline a restorative procedure but wish to preserve their options for the future. This retrospective study reports our experience of conservative proctocolectomy and poses the question: can this operation be recommended in ulcerative colitis?

Patients and methods

Twenty-three patients had a conservative proctocolectomy at this hospital between 1975 and 1987. The colon and rectum were dissected to the level of the pelvic floor and the rectum was transected under upward traction. Using this technique the mucosal transection is close to the dentate line and any residual mucosa can be removed by peranal mucosectomy. The pelvis was drained by a tube drain through the anal canal in 19 patients and by suction drainage from above in four. The case notes have been studied retrospectively to determine the indication for anal conservation, postoperative pelvic and anal complications, and the frequency and outcome of subsequent restoration.

Results

Conservative proctocolectomy was performed for ulcerative colitis in 19 patients, Crohn's disease in three patients and familial adenomatous polyposis in one. There were 13 men and ten women with a median age of 34 years. Most of the patients had this operation because they declined a restorative procedure but wanted to retain their option for a later pouch (*Table 1*).

Uncomplicated healing occurred in only three patients (13 per cent), in one who had Crohn's colitis and in another following removal of an incontinent ileoanal pouch. During the postoperative period, 11 patients developed an anal discharge and nine patients an infected haematoma, which drained on digital examination or through a proctoscope. Infected haematomas were unrelated to the type of pelvic drainage employed.

Six of the 11 patients with an anal discharge had no further treatment and the discharge ceased in four after 24, 30, 36 and 36 months, and persisted in two after 9 and 38 months. The remaining five patients, together with all nine with an infected haematoma, developed chronic pelvic sepsis. The characteristic finding in these patients on digital examination was a normal anal canal closed at its upper end except for a small sinus into a pelvic cavity. The cavity could be confirmed radiologically (*Figure 1*).

Management of the sepsis that occurred in 14 patients is detailed in *Figure 2*. One patient healed with no further treatment but a total of 22 operations were performed on the other 13 patients. Two patients had an ileoanal pouch anastomosis. In both patients the operation was recorded as being technically difficult One patient was lost to follow-up abroad and the other had a good result, emptying the pouch spontaneously five times daily but with some nocturnal soiling. Curettage was performed, under general anaesthetic, in the remaining 11 patients but failed to eradicate the sepsis. Six patients went on to division of the anal sphincter in an attempt to provide drainage of the pelvic cavity. Sepsis was eradicated in one patient by sphincter division, two patients healed after excision of the anal canal for sepsis persisting despite sphincter division, and three have continuing sepsis The current outcome of these patients is summarized in *Table 2*.

Discussion

After intersphincteric dissection of the anal canal with primary suture of the perineal wound, primary healing occurs in about

Table 1 *Indications for performing a conservative proctocolectomy*

	No. of cases
Possible later pouch	15
Carcinoma in ulcerative colitis	2
Possible Crohn's disease	3
Failed ileoanal pouch	
Ischaemia	1
Incontinence	1
Pelvic sepsis	1
Total	23

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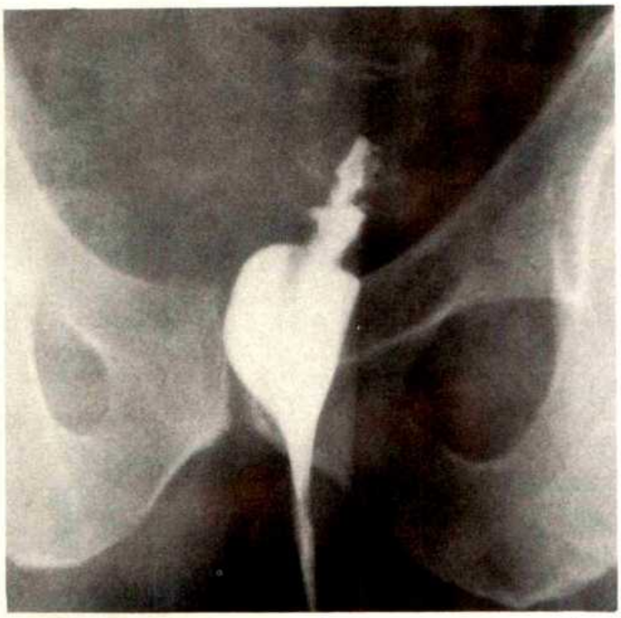

Figure 1 *Sinogram of a patient with pelvic sepsis showing a pelvic cavity above the normal anal canal*

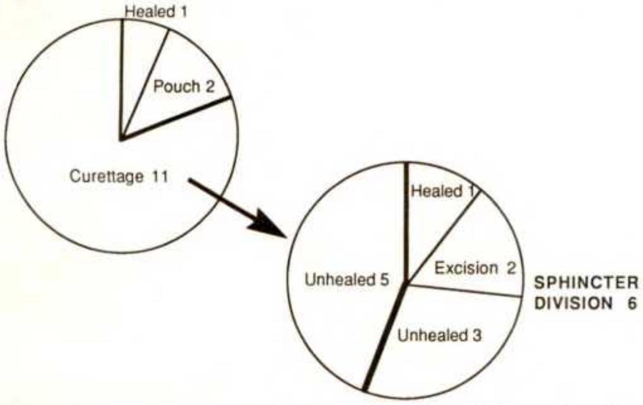

Figure 2 *Management of 14 patients with pelvic sepsis after conservative proctocolectomy*

Table 2 *Long-term outcome of 23 patients after conservative proctocolectomy*

	No. of cases	Time to healing or duration of follow-up (months)
Healed		
Primary healing	3	
Delayed healing	5	12, 24, 30, 36, 36
After sphincter division	1	12
After anal excision	2	12, 36
Anal discharge	2	9, 38
Current sepsis		
Curettage	5	12, 17, 24, 54, 86
Sphincter division	3	18, 36, 72
Later pouch	2	6, 19

50 per cent of patients and in 82 per cent the wound will be healed within 12 months of surgery[5]. The uncomplicated healing in only 13 per cent in this series after conservation of the anal canal compares unfavourably with this. None of these patients had perineal sepsis preoperatively. Postoperative sepsis was unrelated to the type of drain used. Ultimately, healing occurred in 11 patients (48 per cent) at intervals from 12 to 36 months (median 28 months) after the proctocolectomy, but only after sphincter division in one and sphincter division and anal excision in two.

Only two patients have subsequently had a restorative ileoanal anastomosis. Obviously, the optimal time to perform a restorative procedure is before the sphincter is damaged either by sepsis or by attempts to eradicate that sepsis. The procedure was difficult to perform in these two patients because of scarring in the pelvis, but there were no problems in completion of the anastomosis. Neither patient had any septic complications postoperatively and both have had their ileostomy closed. One of the concerns about pelvic sepsis in restorative proctocolectomy is the adverse effect of the resulting fibrosis and scarring on evacuation and control of the pouch. Two recent studies have suggested that once sepsis has been eradicated the function of the pouch is not usually compromised[6,7] unless an anastomotic stricture develops, in which case there is a higher chance of being unable to evacuate the pouch spontaneously[8].

Pelvic sepsis caused significant morbidity in 11 patients. Unlike the sepsis that sometimes follows intersphincteric excision of the anus, drainage of pus from the pelvic cavity is inadequate through the anal canal. This probably accounts for persistence of sepsis after drainage of a postoperative haematoma and for the failure of curettage to expedite healing. Sphincter division alone was unsuccessful in eradicating the sepsis in five of six patients, and two went on to intersphincteric excision of the anal canal. Once the sphincter has been divided, restoration will be impossible and it might be advisable to proceed immediately to anal excision when chronic sepsis has become established, unless restoration is indicated at that time.

Conservation of the anus is not without its complications. With only two patients proceeding to restorative ileoanal anastomosis, we cannot draw any firm conclusions about whether this is a viable option but if 'early' restoration is contemplated it would seem advisable to perform it at the initial operation. There is recent evidence that coexisting adenocarcinoma is not a contraindication to ileal pouch–anal anastomosis at the time of the initial resection[9]. If restoration is anticipated as a 'late' option, dissection below the peritoneal reflection should be avoided retaining a short rectal stump. If retention of a short rectal stump is contraindicated, a conventional intersphincteric dissection of the anal canal is advisable although the anal canal could be conserved if the patient is fully aware of the likelihood of chronic anal discharge or pelvic sepsis. These complications are incompatible with the desire of many patients to undergo the procedure that 'offers the best guarantee of trouble-free return to normal life and employment'.

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Multivariate analysis of factors influencing the results of restorative proctocolectomy

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Univariate and multivariate analyses have been used to assess the influence of 14 variables on the results of 65 consecutive ileoanal pouch procedures over 5 years. There were nine failures requiring intubation, ileostomy or pouch excision. There was a significant association between failure and pelvic sepsis ($P<0{\cdot}05$, $n=8$), endoanal mucosectomy ($P<0{\cdot}05$, $n=7$), preservation of a long rectal cuff ($P<0{\cdot}05$, $n=5$) and lack of experience with the operation ($P<0{\cdot}05$, $n=8$). Of 49 patients with preoperative evidence of ulcerative colitis, three are now known to have Crohn's disease. Functional outcome was significantly impaired in patients who developed pelvic sepsis ($P<0{\cdot}01$) or a postoperative fistula ($P<0{\cdot}05$), and who had an endoanal mucosectomy ($P<0{\cdot}05$). Success with ileoanal pouch reconstruction increases with experience. Avoidance of sepsis is associated with a lower failure rate, improved functional results and reduced hospital stay. Preliminary colectomy is also advised to exclude Crohn's disease if the diagnosis is in question.

Keywords: Restorative proctocolectomy, morbidity, complications, functional results, factors, pelvic sepsis

Restorative proctocolectomy with ileonal–pouch anastomosis has been used in the UK since 1976 for the treatment of ulcerative colitis and familial adenomatous polyposis[1]. We have also found that the operation may be used for patients with severe megacolon and megarectum associated with stasis and obstruction. During this time there have been various modifications in surgical technique. These include the design of the pouch[2–5], the extent of rectal resection[6–8], the need to divide mesenteric vessels to achieve adequate length of the pouch[9], and techniques that minimize damage to the anal sphincters and pelvic floor[10]. In addition to all these factors is the acquisition of personal skills with the procedure[3,4]. We have used univariate and multivariate analyses to examine the influence of various factors on success, postoperative complications and functional results in our first 65 patients. The factors studied are listed in *Table 1*.

Methods

Analyses

The data are derived from all patients having a restorative proctocolectomy in this hospital who have been followed up for more than 6 months after restoring intestinal continuity.

All patients with a functional pouch were interviewed personally and examined in June and July 1988. Frequency of defaecation during the day and at night in the month before interview was recorded on a diary card. A functional score (0–12) recorded the presence or absence of 12 variables. The functional score was based on discussions with other colleagues engaged in evaluating results of restorative proctocolectomy. The functional score was derived by assigning a single point to the following functions: daily frequency >5, daily frequency >7, nocturnal frequency >1, urgency, soiling during the day, soiling at night, incontinence, failure of discrimination, use of antidiarrhoeals, dietary restriction, and use of pads during the day and at night. A postoperative complication score (0–8) recorded postoperative bleeding, wound and pelvic sepsis, anal stenosis, anal or pouch cutaneous fistula, intestinal obstruction and 'pouchitis'. Failure was defined by one of three criteria: the need for intubation (stricture, $n=1$), the need to raise an ileostomy after previous closure (severe diarrhoea, $n=1$) or excision of the pouch (sepsis, infarction, fistula, diarrhoea or unacceptable functional results, $n=7$).

Univariate analysis used the Mann–Whitney *U* test or Fisher's exact test. Multivariate analysis using principal components and Fisher's linear discriminant analysis was performed to identify the variables that predisposed to complications, poor functional results or failure.

Surgical variables

Restorative proctocolectomy was either a one-stage procedure ($n=36$) or performed after a previous emergency colectomy ($n=29$): 12 had mucous fistula, 13 had a long rectal stump oversewn, but in four cases the rectal stump was closed at the level of the levator ani.

Table 1 *Restorative proctocolectomy variables*

Variable	No. of cases ($n=65$)
Age (median 31 years)	
Sex	
Female	36
Male	29
Previous colectomy	29
Covering ileostomy	46
Rectal cuff preservation	14
Endoanal mucosectomy	17
Pouch design	
S	2
J	46
W	17
Diagnosis	
Ulcerative colitis	45
Polyposis coli	8
Megarectum	8
Crohn's disease	4
Vascular mobilization	42
Experience*	33
Complications	
Pelvic sepsis	16
Anal stenosis	12
Fistula	9
Obstruction	9

* Last 33 (50 per cent) cases compared with first 32

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In the earlier part of this series the rectum was mobilized using a long perimuscular procedure, the superior haemorrhoidal artery was preserved, and the rectum was often divided 2–3 cm above the pelvic floor ($n = 14$) However, as the pelvic autonomic nerves can be identified and preserved even after pedicle ligation of the superior haemorrhoidal vessels, the entire rectum is now excised with the mesorectum to the pelvic floor with the superior haemorrhoidal vessels ($n = 51$).

In the early part of this series the anorectal mucosectomy was performed entirely as an intra-anal procedure using a Parks' anal speculum ($n = 17$) During the past 2 years, since adopting the practice of complete rectal excision, anal mucosectomy has been performed in continuity with the rectum to avoid potential damage to the anal sphincters ($n = 48$).

With the exception of two early patients having a triple lumen S pouch, pouch construction has either been with the double lumen J pouch ($n = 46$) or the quadruple W pouch ($n = 17$)

Initially little attention was taken over dividing vessels in the small bowel mesentery ($n = 23$), and consequently some anastomoses were performed under tension and eight were complicated by stricture. A more extensive vascular mobilization is now used ($n = 42$) The origin of the superior mesenteric vessels is freed from the duodenum and the pancreas The terminal ileal arcades are carefully preserved, but proximal vessels preventing adequate distal mobilization are divided provided the peripheral arcades are intact. Occasionally the superior mesenteric pedicle has been divided if adequate length could not be achieved by other means Using this technique, only four strictures have been recorded but one pouch became ischaemic

In this series the ileoanal anastomosis was invariably sutured, using interrupted 3–0 Vicryl® (Ethicon Ltd, Edinburgh, UK) on a strong half-circle needle either at ($n = 56$) or 2 cm proximal to ($n = 9$) the dentate line None of the ileoanal anastomoses were stapled in this series.

Results

Eight patients had familial adenomatous polyposis. Eight patients with megarectum could not defaecate after a previous subtotal colectomy and ileorectal anastomosis The remaining 49 patients had inflammatory bowel disease of whom four are now known to have Crohn's disease

Failures

Nine patients have been classified as failures The details of these patients are listed in *Table 2*.

The failure rate in the first half of the study (25 per cent) was significantly higher than in the second half of this series (3 per cent; Fisher's exact test, $P < 0.02$). Eight of the failures had pelvic sepsis. Two failures were associated with Crohn's disease Seven of the nine failures had an endoanal mucosectomy, five being associated with the retention of a long rectal cuff; in two abdominal mucosectomy was impossible because the rectal stump had been divided at the level of the levator ani

Multivariate analysis indicated that failures were significantly greater after endoanal mucosectomy ($P < 0.05$), retention of the rectal cuff ($P < 0.05$), pelvic sepsis ($P < 0.05$) and surgical inexperience ($P < 0.05$)

Complications

Complications occurred in 25 patients (45 per cent) and are listed in *Table 3* In the first half of the series 19 patients developed complications (59 per cent) compared with ten in the second half (30 per cent); the difference is not significant

Bleeding. Two patients bled from within the sleeve of a long rectal cuff; both eventually had their pouch excised. One episode of bleeding was due to over-anticoagulation, the other was a secondary haemorrhage from sepsis

Sepsis. Despite the use of perioperative antibiotic cover, 21 patients developed postoperative sepsis (32 per cent). Eleven patients developed wound infections. Sixteen operations were complicated by pelvic sepsis (25 per cent). Eight of the 16 patients with pelvic sepsis were in the group classified as failures.

Table 3 *Complications*

Complication	No of cases
Bleeding	2
Wound sepsis	11
Pelvic abscess	16
Anal stenosis	12
Anovaginal fistula	3
Enterocutaneous fistula	6
Intestinal obstruction	9
Pouchitis	6
Clostridium difficile diarrhoea	2

Table 2 *Data on surgical failures*

No in series	Follow-up (months)	Age (years)	Diagnosis	Pouch	PC	VM	CI	EM	LRC	PS	AS	F	Functional score
1	54	32	UC	S	+	–	+	+	+	+	–	–	10
2	48	31	UC (?RE)	J	+	–	+	+	+	+	+	+	10
7	41	31	RE	J	+	–	+	+	+	+	–	+	11
8	40	18	UC	J	+	–	+	+	+	+	–	–	12
10	32	41	UC	J	–	–	+	+	+	+	–	–	*
21	18	42	RE	J	–	+	+	–	–	–	–	–	8
23	17	27	UC	J	+	+	+	+	–	+	+	+	11
25	14	23	UC	J	+	+	+	+	–	+	+	+	10
41	8	31	UC	W	+	+	+	–	–	+	–	–	*

No. in series	Problem	Result
1	Failure to evacuate, incontinent, long efferent limb, stenosis	Pouch excision (24 months)
2	Anovaginal fistula repair, stenosis	Intubation (6 months)
7	Enterocutaneous fistula, incontinent, persistent sepsis	Pouch excision (10 months)
8	Intestinal obstruction, infarction + resection, diarrhoea	Loop ileostomy (10 months)
10	Bleeding in rectal cuff – anticoagulated, sepsis	Pouch excision – emergency (21 days)
21	Severe diarrhoea	Pouch excision (12 months)
23	Enterocutaneous fistula, stenosis, incontinent	Pouch excision (10 months)
25	Enterocutaneous fistula, stenosis, incontinent	Pouch excision (12 months)
41	Ischaemic pouch and distal small bowel, tight trephine for loop ileostomy	Pouch excision (13 days)

* Unevaluable because intestinal continuity was not restored. UC, ulcerative colitis; RE, regional enteritis (Crohn's disease), PC, previous colectomy, VM, vascular mobilization, CI, covering ileostomy, EM, endoanal mucosectomy; LRC, long rectal cuff, PS, pelvic sepsis; AS, anal stenosis, F, fistula

Stenosis. Twelve patients developed stenosis at the ileoanal anastomosis (18 per cent); in one case this was present preoperatively from previous sepsis. Two strictures occurred after successful repair of anovaginal fistula. Eight of the strictures were associated with pelvic sepsis when there had been no attention to mesenteric vascular mobilization Four patients with strictures were classified as failures; the remaining eight patients have been successfully managed by gentle dilatation.

Fistula. There were nine fistulae, three from the pouch–anal anastomosis to the vagina and six enterocutaneous fistulae. However, three of the six enterocutaneous fistulae occurred after pouch construction from small bowel damaged at laparotomy ($n=1$) or ileostomy closure ($n=2$); all of these fistulae closed spontaneously. Of the remaining enterocutaneous fistulae two occurred from the ileoanal anastomosis (both requiring pouch excision) and one from the closed end of the ileum in a patient later discovered to have Crohn's disease requiring pouch excision.

Obstruction. Nine patients developed intestinal obstruction One patient with obstruction was designated a failure due to a small bowel infarction 10 months after operation, which required extensive resection. Five of the nine patients with intestinal obstruction required a laparotomy, one of whom developed an enterocutaneous fistula from operative damage (see above).

'Pouchitis'. Only six patients in this series developed 'pouchitis' (9 per cent). All presented with severe diarrhoea, four had joint pains and fever with systemic illness. All patients had some degree of anal stenosis at the onset of symptoms. All patients responded to oral metronidazole but one relapsed after discontinuing therapy.

Clostridium difficile diarrhoea. Two patients with severe diarrhoea were found to have *C. difficile* on stool culture. Neither case was associated with cytotoxin and both improved with vancomycin therapy.

Multivariate analysis indicated that the only factor to be associated with a significant increased complication rate was endoanal mucosectomy ($P<0{\cdot}05$).

Hospital stay

Total hospital stay ranged from 12 to 62 days (median 21 days). Using a multivariate analysis, the following factors were significantly related to prolonged hospital stay: preservation of the rectal cuff, extent of vascular mobilization, method of mucosectomy, experience of the surgeon, pelvic sepsis, anal stenosis and postoperative fistula ($P<0{\cdot}05$).

Function

Functional results were available in only 63 patients because two patients had had early pouch excision. The functional results have been included in the seven additional patients who are now classified as failures (*Table 4*).

Table 4 *Functional results*

	No. of cases	No. of failures
Frequency >7/day	14	2
Frequency >1/night	26	6
Urgency	3	1
Soiling by day	3	2
Soiling at night	9	3
Incontinence	6	4
Failure of discrimination	7	2
Use of antidiarrhoeal agents	31	7
Dietary restriction	10	5
Use of pads by day	4	4
Use of pads at night	11	5
Total	63	7

Two patients (both failures) had early pouch excision and could not be evaluated

One of the principal components of the functional score was frequency of defaecation, which varied considerably with duration of follow-up. A median frequency of seven bowel actions per day and twice at night was recorded in the first 6 months after ileostomy closure. By contrast, the median frequency 12 months after ileostomy closure was only five times per 24 h and after 24 months was only four times in 24 h. Median frequency of defaecation was five times in 24 h after J pouch construction compared with four times in 24 h in patients with a W pouch. Pelvic sepsis influenced stool frequency, the median frequency being eight bowel actions in 24 h in 16 patients who developed pelvic sepsis compared with four stools per 24 h in the remainder (Fisher's exact test, $P<0{\cdot}05$).

Analysis of the 56 patients who were not classified as failures indicated that soiling occurred in only one patient during the day but six patients leaked at night. Only two patients have episodes of frank incontinence. Six patients need to wear pads at night but none during the day. Twenty-four patients continue to take antidiarrhoeal agents (43 per cent) but only five need to restrict their diet (9 per cent).

When functional scores were analysed in all patients by multivariate analysis, only pelvic sepsis and endoanal mucosectomy ($P<0{\cdot}05$) significantly influenced the functional outcome. Both soiling and the use of pads were significantly more common in patients having endoanal mucosectomy ($P<0{\cdot}05$) and in those developing pelvic sepsis ($P<0{\cdot}01$). There was no evidence that age or previous colectomy had any adverse influence on functional outcome.

Discussion

In international terms this is a small series of ileoanal–pouch anastomoses[11–17]. Unlike the two other UK centres with a comparable experience of restorative proctocolectomy[18,19], the series in question spans only 5 years. The St. Mark's Hospital experience includes three different pouch designs, and operations by at least three different surgeons spanning the last 10 years[20]. The Leeds experience is only a little shorter and includes straight ileoanal anastomoses, at least three different pouch designs and variable preservation of the anal transition zone[21]. The purpose of this review has been to analyse the influence of changes in surgical technique and experience in a consecutive group of 65 patients operated on by one person.

This multivariate analysis has confirmed the overwhelming importance of pelvic sepsis and total rectal excision on complications, functional results and hospital stay. By contrast, pouch design, previous colectomy, age and the sex of the individual had no apparent influence on the results. There was a significant association between failure and pelvic sepsis, endoanal mucosectomy, retention of a long rectal cuff and experience with the operation.

Crohn's disease was associated with failure in two out of four cases. The diagnosis of Crohn's disease was associated with fistula and sepsis in one patient and incapacitating diarrhoea in another, but there are two patients with known Crohn's disease who have had an excellent functional result for over 3 years. Despite preoperative endoscopic biopsies the ultimate diagnosis of Crohn's disease was made from colectomy specimens in three patients and only from the excised pouch in the other. As previous colectomy has been shown to have no adverse effect on complications and the functional score, we believe that preliminary colectomy should be advised if the diagnosis of ulcerative colitis is in doubt. Under these circumstances, construction of a mucous fistula or oversewing the rectum well above the sacral promontory makes subsequent rectal excision much easier. The resection specimen should be scrutinized by an experienced histopathologist. No failures occurred in patients with polyposis or megarectum.

Age does not seem to be a specific contraindication to restorative proctocolectomy and three patients over 55 years of age have had excellent functional results. Motivation, personality and perhaps intelligence are important considerations in selection of patients.

Restorative proctocolectomy is not suitable for all patients with ulcerative colitis[20,22]. During this experience, 17 patients have undergone conventional proctocolectomy because they were considered unsuitable for this procedure. The reasons for conventional surgery were age greater than 60 years in three, severe psychiatric disease in four, preference for conventional ileostomy even after counselling in four, perianal disease in one, low IQ in two, and an over-riding desire to return to work with minimal delay in three. In our view the group of patients with ulcerative colitis who are most suitable for a restorative procedure are those with a short history of disease requiring emergency colectomy. All of these patients should be offered counselling from a patient who has had a successful pouch as well as from patients with a well functioning ileostomy.

The quadruple pouch has a larger capacity and is more compliant than the triple or double lumen pouches[23,24], consequently frequency of defaecation is less[25,26]. However, in our experience, postoperative complications and functional results were similar when the J and W pouch were compared. In this study pelvic sepsis had a profound influence on pouch function[27] and is probably more important than pouch design.

The 19 patients who did not have a covering loop ileostomy are of some interest. Although there were no complications, severe postoperative diarrhoea led to a prolonged hospital stay in four patients. Nevertheless, hospital stay was reduced to a median of 16 days by avoiding a proximal stoma. Although a successful outcome is possible without a loop ileostomy[28], some patients suffered transient severe diarrhoea, which may be psychologically damaging early after operation. On the other hand, the dangers of closing a loop ileostomy are avoided[29,30].

Considerable care and judgement must be exercised in deciding when to reoperate for intestinal obstruction; unnecessary laparotomy carries the risk of damaging the small bowel whilst delayed management resulting in infarction may compromise any hope of an acceptable functional result. Iatrogenic enterocutaneous fistulae from surgical damage or ileostomy closure all resolved with conservative therapy. All three pouch–cutaneous fistulae required pouch excision, one because of Crohn's disease, the others because of anal stenosis. Two of the three anovaginal fistulae were associated with a high anal anastomosis and sepsis resulting in suprasphincteric fistulae. The other was a late fistula from an anal gland infection. All were successfully repaired, but two patients developed anal stenosis.

In our view, pelvic sepsis has been the factor of greatest prognostic importance in determining poor function and potential failure. Pelvic sepsis was more common in the earlier part of this series when extensive vascular mobilization was not used and a long rectal cuff was retained[31]. We believe that it may be necessary to divide up to three major vessels in order that the apex of the pouch can reach the dentate line without being under any tension[32]. However, there is a small risk of infarction. Abdominal mucosectomy itself may not be critical in achieving improved functional results but endoanal mucosectomy can be associated with soiling if there has been prolonged anal retraction.

These data emphasize the learning curve of surgeons undertaking restorative proctocolectomy for the first time. We would argue, therefore, that the operation should be confined to a few centres capable of gaining wide experience of the operation so that interested surgeons can be taught to perform the operation safely. Audit of our results suggests that avoidance of pelvic sepsis by complete rectal excision and abdominal mucosectomy has been associated with improved functional results. If the underlying diagnosis is in question, we would now advise a preliminary colectomy, as function is not impaired by constructing a pouch as a secondary procedure.

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Case report

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Familial polyposis: colon cancer in the absence of rectal polyps

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It is widely believed that rectal polyps presage colonic polyps in the familial polyposis syndrome (FPS). Accordingly, rigid proctosigmoidoscopy has been justified as the sole means of presymptomatic detection of polyps in FPS[1]. We report a case of FPS with multiple colonic polyps, adenocarcinoma in the transverse colon, and a rectum macroscopically free of polyps.

Case report

An asymptomatic 39-year-old woman with a family history of FPS was referred for a routine examination. There was an osteoma 6 × 8 mm in the right temporal bone The rigid proctosigmoidoscope could not be inserted beyond 17 cm. The rectal mucosa was macroscopically normal. Two small polyps were seen in the distal sigmoid at 17 cm. Colonoscopy revealed scattered polyps in the sigmoid colon, with increasing numbers proximally, and more than 200 in the ascending colon. A prophylactic subtotal colectomy with ileorectal anastomosis was performed. In the resected specimen, myriad 0·1–0·5-cm polyps covered the mucosa of the proximal colon. There were fewer polyps more distally, and only ten in the distal 4 cm of the specimen. Microscopy showed adenomatous polyps and multiple foci of adenomatous change. There was also a 1·5 × 1·7-cm ulcerated, sessile, moderately well differentiated adenocarcinoma in the mid-transverse colon, infiltrating submucosa to the muscularis propria No lymph node metastases were found.

Discussion

Data on the distribution of polyps in FPS come from Bussey[2]. In 18 colectomy specimens, polyps showed a predilection for the left colon. The rectum was not examined. However, in 39 per cent of the cases, there was a greater number and density of polyps proximal to the splenic flexure.

Three large series have reported the apparent universal occurrence of rectal polyps in FPS patients with multiple colonic polyps. In two, the diagnosis was based solely on proctosigmoidoscopic findings[2,3]. Cases with colonic polyps in the absence of rectal polyps would not have been diagnosed until rectal polyps appeared. In the third, negative proctosigmoidoscopy was followed by a double contrast barium enema[4]. This examination is negative in about 75 per cent of cases where polyps are found at colonoscopy[5,6].

Several reports of FPS have alluded to rectal sparing in the presence of multiple colonic polyps[7,8]. Most notably, Harvey *et al.*[9] described 34 patients from FPS families. Four had no rectal polyps, and two of those had colon cancer at the time of diagnosis. In the Mayo Clinic series of 178 patients with multiple polyposis, 35 had no rectal polyps[10,11]. While some of these patients may not have had FPS, one of the 35 had a family history of FPS and nine had more than 100 colonic polyps.

The conclusion that cancer may develop before polyps appear in the rectum has profound implications for the selection of procedures for screening FPS families. The limited area of colorectal mucosa accessible through the rigid proctosigmoidoscope and the variability in the distribution of polyps in FPS suggest that flexible sigmoidoscopy or colonoscopy should be the screening procedure of choice for early detection of colorectal polyps in members of FPS kindred.

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Operative mortality following surgery for colorectal cancer

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From 1973 to 1986 at the Baviere Hospital, University of Liège, 476 patients underwent surgery for colorectal cancers. The overall operative mortality rate was 13·4 per cent. The following postoperative life-threatening complications occurred: myocardial infarction (14 per cent of the postoperative deaths) during the first three postoperative days; bronchopneumonia (27 per cent of the postoperative deaths) mainly during the first postoperative week; pulmonary embolism (17 per cent of the postoperative deaths) mainly during the second postoperative week, anastomotic leakage and cerebrovascular accident (14 and 8 per cent of the postoperative deaths respectively) mainly during the third and fourth postoperative weeks. Specific risk factors were chronic obstructive airways disease associated with a higher incidence of postoperative bronchopneumonia, and previous myocardial infarction associated with postoperative myocardial infarction and pulmonary embolism. General risk factors were old age and emergency procedure, both of which were associated with a higher incidence of infectious complications. The operative mortality rate fell from 20·1 per cent in the 1973–79 period to 7·8 per cent in the 1980–86 period.

Keywords: Colorectal cancer surgery, postoperative complications, operative mortality

Surgical resection is the only curative treatment in colorectal cancer; resection of the tumour may improve the quality of life in advanced incurable disease. Thus an increased operability and resectability rate should be the first step towards an improvement in the survival rate and the quality of life of these patients[1–6,13]. Others have reported that despite the increased number of aged and debilitated patients undergoing surgical treatment there has been an improvement in operative mortality recently[2,3]. We therefore decided to investigate whether this reduction in perioperative mortality rate had occurred in our institution. A retrospective analysis of patients operated on between 1973 and 1986 was made. Risk factors were reassessed and the type and timing of postoperative life-threatening complications were related to postoperative mortality. Two 6-year periods were compared: 1973–79 and 1980–86.

Patients and methods

From 1973 to 1986 at the Baviere Hospital, University of Liège, 476 patients (210 women, 266 men) underwent surgery for colorectal cancer. The mean age was 68 (standard deviation 6) years. In all, 48 left hemicolectomies, 68 right hemicolectomies, 14 transverse colectomies, 83 sigmoid colectomies, 32 segmental resections, 59 anterior resections, 75 abdominoperineal resections, 28 Hartmann's procedures, six total colectomies and 63 palliative operations were performed. All deaths in hospital occurring after surgery were considered as operative mortality. Age, antecedent hypertension, cardiac rhythm disorders, myocardial infarction, diabetes, renal insufficiency and chronic obstructive airways disease were considered risk factors. Postoperative bronchopneumonia, pulmonary embolism, myocardial infarction, anastomotic leakage with intra-abdominal sepsis and cerebrovascular accidents were considered postoperative life-threatening complications. The χ^2 test with Yates' correction was used for analysis of the data.

Results

Operative mortality

Of 476 patients, 64 postoperative deaths were observed between 1973 and 1986. Thus the overall operative mortality rate was 13·4 per cent. As shown in *Tables 1* and *2*, the principal cause was bronchopneumonia (27 per cent) occurring during the first postoperative week. The other aetiologies included: pulmonary embolism (17 per cent) which occurred during the second postoperative week, myocardial infarction (14 per cent) which occurred during the first three postoperative days, sepsis related to anastomotic leakage (14 per cent), most cases of which occurred during the third and fourth postoperative week, cerebrovascular accident (8 per cent) which also represented a late complication, multisystem organ failure related to preoperative peritonitis (5 per cent), all cases of which occurred during the first two postoperative days.

General risk factors

Preoperative status. One hundred and twelve patients (23·5 per cent) suffered from hypertension before their operation. Other pre-existing conditions were diabetes (27 cases, 5·7 per cent), chronic obstructive airways disease (30 cases, 6·3 per cent), previous myocardial infarction (24 cases, 5·0 per cent), renal insufficiency (7 cases, 1·5 per cent) and rhythm disorders (14 cases, 2·9 per cent). No significant differences in surgical mortality could be found between patients with none, one or two pre-existing diseases, operative mortality rate increased only in the small group of patients suffering from three preoperative disorders (*Table 3*).

Table 1 *Causes and numbers of deaths in 476 patients from 1973 to 1986*

Cause of death	No. of patients	Percentage
Bronchopneumonia	17	27
Pulmonary embolism	11	17
Myocardial infarction	9	14
Anastomotic leakage	9	14
Cerebrovascular accident	5	8
Preoperative peritonitis	3	5
Mesenteric infarction	1	2
Stress ulcer	1	2
Unknown	8	12
Total	64	13·4

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Table 2 *Timing of operative complications and related deaths*

Type of complication	Day of diagnosis (days after surgery)	Day of death (days after surgery)
Preoperative peritonitis	0	1 (1)
Myocardial infarction	2 (1)	8 (6)
Bronchopneumonia	6 (4)	10 (5)
Pulmonary embolism	10 (5)	14 (8)
Cerebrovascular accident	17 (10)	25 (15)
Anastomotic leakage	20 (12)	27 (16)

Mean values are given with standard deviations in parentheses

Table 3 *Surgical mortality related to four classes of preoperative status*

No of preoperative diseases	No of patients	No. of deaths
0	295	36 (12·2)
1	137	16 (11·7) (χ^2 = 0·0001)*
2	36	7 (19) (χ^2 = 0·92, P < 0·4)*
3	8	5 (62) (χ^2 = 12·81, P < 0·0005)*
Totals	476	64 (13·4)

Values in parentheses are percentages. * Compared with patients having no preoperative diseases

However, two risk factors, chronic obstructive airways disease and antecedent myocardial infarction, were specifically correlated with an increase in postoperative life-threatening complications.

Age. The mean age of patients in the whole series was 68 years *versus* 74 years in the group of patients who died. The patients were divided into four age groups defined relative to the standard deviation of the whole series which was 6 years; there was no significant difference in mortality rate between patients younger than 62 years and those between 62 and 68 years However, there was a twofold increase in mortality in patients aged between 69 and 74 years (χ^2 = 6·78, P < 0·01) and a fourfold increase in those over 74 years (χ^2 = 24·66, P < 0·0005; *Table 4*).

In an attempt to dissociate age from the impact of pre-existing diseases, the surgical mortality was compared in two age groups with a similar preoperative status; for each definite preoperative risk factor, there was a higher mortality rate in the patients older than 69 years than in younger patients (*Table 5*).

Emergency procedures. Emergency surgery was performed in 62 patients (13·0 per cent): obstruction occurred in 44 patients and perforation in 18 patients. An increased operative mortality rate was associated with emergency procedures in comparison with elective procedures: 26 *versus* 11·6 per cent (χ^2 = 8·20, P < 0·005). This was related to a higher incidence of infection, anastomotic leakage (χ^2 = 9·61, P < 0·005) and bronchopneumonia (χ^2 = 5·44, P < 0·025) in these patients (*Table 6*).

Types and sites of resection. There is no significant difference in operative mortality between the different types of intervention, except for Hartmann's procedure which is associated with a surgical mortality rate of 35·7 per cent (28 patients, ten deaths). In our series, the Hartmann's procedure was performed only in poor-risk cases: among the 28 patients, 12 (43 per cent) were emergency procedures and 16 (57 per cent) were more than 74 years of age. The risk of anastomotic leakage was related to the site of anastomosis: four out of 102 right anastomoses (3·9 per cent) *versus* 31 out of 202 left anastomoses (15·3 per cent; χ^2 = 7·60, P < 0·01).

Specific risk factors and life-threatening complications

Bronchopneumonia occurred in 60 patients (12·6 per cent) with a 28 per cent mortality rate (17 patients). Patients with antecedent chronic obstructive airways disease had a higher incidence of postoperative bronchopneumonia (43 *versus* 10 per cent; χ^2 = 24·55, P < 0.0005) with a higher mortality rate (69 *versus* 17 per cent; χ^2 = 11·22, P < 0·001) than patients without lung disease.

Pulmonary embolism occurred in 11 patients (2·3 per cent) with a 100 per cent mortality rate. The patients with a past history of myocardial infarction had a higher incidence of postoperative pulmonary embolism than patients without this antecedent: 12 *versus* 2 per cent (χ^2 = 7·35, P < 0·01).

Myocardial infarction occurred in 14 patients (2·9 per cent) with a 64·3 per cent mortality rate (nine patients). There was a higher incidence (12·5 *versus* 2 per cent χ^2 = 4·95, P < 0·05) and a higher mortality rate (100 *versus* 54 per cent) of postoperative myocardial infarction in the group with a previous history of myocardial infarction.

Anastomotic leakage occurred in 35 patients (7·3 per cent) with a 26 per cent mortality rate (nine patients) related to sepsis and multisystem organ failure. Thirty-one patients had an anastomosis of the left colon and four had a right colon anastomosis.

Cerebrovascular accidents occurred in five patients (1·0 per cent) with a 100 per cent mortality rate. The mean age was 81 years; three of these five patients had a past history of

Table 4 *Surgical mortality in four age classes*

Age class (years)	No of patients	No. of deaths	Surgical mortality rate (%)
<62	140	7	5·0
62–68	123	9	7·3 (χ^2 = 0·28, P < 0·6)*
69–74	101	16	15·8 (χ^2 = 6·78, P < 0·01)*
>74	112	32	28·6 (χ^2 = 24·66, P < 0·0005)*
68 ± 6 years†	476	64	13·4

* Compared with patients <62 years, † mean ± s.d.

Table 5 *Surgical mortality in two age classes for a definite preoperative state*

	⩽68 years		⩾69 years	
Pre-existing condition	No. of patients	No. of deaths*	No of patients	No. of deaths*
None	143	7 (4·9)	89	14 (16) (χ^2 = 6·56, P < 0·025)*
Emergency procedure	24	2 (8)	38	14 (37) (χ^2 = 4·84, P < 0·05)*
Myocardial infarction	11	1 (9)	13	3 (23)
Chronic obstructive airways disease	11	2 (18)	19	8 (42)
Totals	189	13	159	38

Morality rates given in parentheses. * Compared with patients ⩽68 years cerebrovascular disease and all five patients suffered with poorly controlled arterial hypertension.

Multisystem organ failure due to preoperative peritonitis occurred in three patients (0·6 per cent) with a 100 per cent mortality rate; the mean age was 81 years.

Changes in operative mortality

From 1973 to 1979, 44 patients out of 219 died (20·1 per cent); this was significantly different ($\chi^2=13{\cdot}06$, $P<0{\cdot}0005$) from the period 1980–86 during which there were 20 deaths in 257 patients (7·8 per cent). Between these two periods, the mean age was unchanged: 66 *versus* 63 years.

However, some other significant changes in the characteristics of the patients were found: (1) a diminished number of emergency procedures: 40 patients (18·3 per cent) from 1973 to 1979 *versus* 22 patients (8·6 per cent) from 1980 to 1986 ($\chi^2=9{\cdot}0$, $P<0{\cdot}005$); (2) a reduced incidence of pulmonary embolism: nine patients (4·1 per cent) from 1973 to 1979 *versus* two patients (0·8 per cent) from 1980 to 1986; (3) an improvement in the treatment of some postoperative complications. While the incidence of postoperative myocardial infarction and bronchopneumonia remained unchanged, the mortality rate associated with these complications was reduced from 100 to 38 per cent and from 55 to 15 per cent ($\chi^2=8{\cdot}63$, $P<0{\cdot}005$) respectively; the incidence and outcome of anastomotic leakage remain unchanged (*Table 7*).

Discussion

The operative morbidity and mortality rates related to colorectal surgery clearly depend on patient selection and underlying pathology (i.e. inflammatory process, diverticular disease or carcinoma)[1,2,7]. Our review from 1973 to 1986 includes 476 patients who underwent surgery exclusively for colorectal cancers.

The main causes of death in our series were similar to those reported in other studies[1,2,5]: myocardial infarction occurring during the first three postoperative days (14·1 per cent of postoperative deaths), bronchopneumonia mainly during the first postoperative week (27 per cent of postoperative deaths), pulmonary embolism mainly during the second postoperative week (17 per cent of postoperative deaths), anastomotic leakage and cerebrovascular accident mainly during the subsequent third and fourth postoperative weeks (14 and 8 per cent of postoperative deaths respectively).

Boyd *et al.*[7] found a relationship between the operative mortality rate and the number of pre-existing conditions rather than age as an isolated factor. We have found no significant difference between patients with none, one or two pre-existing disorders, but there was a higher risk of surgical mortality in older patients compared with younger patients. Life-threatening complications are correlated with specific risk factors rather than with the cumulative effect of any preoperative condition. For instance we found previous chronic obstructive airways disease was associated with a four times higher incidence of and mortality from postoperative bronchopneumonia; previous myocardial infarction was associated with a five times higher incidence of and a two times higher mortality from postoperative myocardial infarction and a seven times higher incidence of postoperative pulmonary embolism. These results confirm those reported by Garibaldi *et al.*[8], Jensen *et al.*[2] and Wightman[6].

There is a higher operative mortality rate and increased incidence of septic complications (bronchopneumonia and anastomotic leakage) associated with emergency procedures[7]; patients with anastomoses involving the left colon are particularly at risk[9–11].

Our improved results from 1980 to 1986 emphasize the importance of systematic antithrombosis prophylaxis by subcutaneous heparin, dextran or epidural anaesthesia[12], and early diagnosis and aggressive treatment of early postoperative complications (myocardial infarction and bronchopneumonia).

Surgical resection is the only curative therapy for colorectal cancers[1–5,13] and a more accurate estimation of operative risks should lead to a more rational perioperative management of poor-risk patients.

Table 6 *Postoperative complications in elective* versus *emergency procedures*

Complication	Elective surgery ($n=414$)	Emergency surgery ($n=62$)
Bronchopneumonia	46 (11·1)	14 (23) ($\chi^2=5{\cdot}44$, $P<0{\cdot}025$)*
Anastomotic leakage	24 (5·8)	11 (18) ($\chi^2=9{\cdot}61$, $P<0{\cdot}005$)*
Pulmonary embolism	9 (2·2)	2 (3)
Myocardial infarction	11 (2·7)	3 (5)

Percentages are given in parentheses. *Compared with elective surgery

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Table 7 *Changes in incidence and outcome of complications*

	1973–79 (219 patients)		1980–86 (257 patients)		
	No. of patients	No. of deaths	No. of patients	No. of deaths	
Pulmonary embolism	9 (4·1)	9 (100)	2 (0·8)	2 (100)	
Myocardial infarction	6 (2·7)	6 (100)	8 (3·1)	3 (37·5)	
Bronchopneumonia	20 (9·1)	11 (55)	40 (15·6)	6 (15)	($\chi^2=8{\cdot}63$, $P<0{\cdot}005$)*
Anastomotic leakage	15 (6·8)	4 (27)	20 (7·8)	5 (25)	

Percentages are given in parentheses. * The two time periods compared

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Idiopathic constipation associated with impaired urethrovesical and sacral reflex function

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Sixteen chronically constipated women (age range 20–66 years) and 29 healthy control subjects (age range 22–53 years) underwent neurophysiological assessment of the integrity of pelvic spinal reflexes. The results were compared with videourodynamic studies and multiport anorectal manometry combined with external anal sphincter electromyography. The neurophysiological assessment consisted of electrical stimulation of the dorsogenital nerve, while recording any evoked reflex activity in the external anal and urethral sphincters with concentric needle and surface electrodes. Of these constipated women, 75 per cent had absence of one or more evoked sacral reflexes (compared with 20 per cent of healthy controls, $P<0{\cdot}05$). Sensory thresholds and motor unit potentials in the external anal sphincter were similar in healthy and constipated women. Nine (56 per cent) constipated women displayed urodynamic abnormalities (increased bladder capacity, acontractile bladder and genuine stress incontinence). Only 38 per cent of constipated women perceived a desire to defaecate during rectal distension with up to 100 ml, compared with 95 per cent of normal subjects ($P<0{\cdot}0005$). Moreover, 73 per cent of constipated women did not relax the external anal sphincter during defaecation, compared with 12 per cent of controls ($P=0{\cdot}001$). Taking into account the possible significance of our data in relation to previous findings it is suggested that the integration of sensory information within the sacral cord may be impaired in chronic idiopathic constipation.

Keywords: Constipation, urology, sphincter

Patients with low spinal cord lesions usually suffer with difficulties in defaecation and micturition. Physiological studies in such patients reveal reductions in sensitivity of the rectum, and impaired reflex control of the external anal sphincter[1]. We were intrigued by the observation that patients with severe constipation often exhibit disturbances in anorectal[2,3] and urethrovesical[4] function that are similar to those seen in patients with low spinal cord lesions. Thus, the aim of this study was to investigate the role of disturbed spinal cord function in the aetiology of severe, chronic idiopathic constipation. This involved testing the integrity of evoked spinal reflexes relaying in the conus medullaris (S2–S4) and examining the relationship between these reflexes and anorectal and urethrovesical function.

Patients and methods

Subjects

Studies were carried out on 16 women, with a mean (s.e.m.) age of 40 (4) years (range 20–66 years), who were referred for investigation of intractable constipation of at least two years' duration. Intractable constipation was defined as the passage of fewer than two stools per week, despite ingestion of laxatives and dietary fibre. Four of these women were nulliparous, the remainder had had between one and four vaginal deliveries (median, two). Each patient had undergone full investigation, including large bowel radiology and thyroid function tests, to exclude local or systemic disease as an underlying cause of their symptoms. Five patients with previously normal bowel habit related the onset of their constipation to abdominal hysterectomy. Six of the 16 patients complained of urinary tract symptoms in addition to their constipation: three patients had urinary incontinence and increased frequency, two had increased frequency alone, and a further patient found it necessary to strain in order to micturate (*Table 1*).

Twenty-nine healthy asymptomatic women matched for age and parity acted as control subjects. Nineteen of these women underwent anorectal studies; ten consented to neurophysiological investigation.

This study received approval by the Sheffield Area Health Authority Ethical Committee; all subjects provided written informed consent.

Methods

Patients and controls underwent a series of investigations which included neurophysiological studies of evoked sphincter responses following electrical stimulation of the dorsogenital nerve, videourodynamic assessment of urethrovesical function, combined anorectal manometry and external anal sphincter electromyography, tests of rectal sensation, and defaecation studies using simulated stools.

Neurophysiological tests of spinal reflexes. Electrical stimulation of the dorsogenital nerve elicits a reflex contraction in the bulbocavernosus, external anal sphincter and urethral sphincter that is mediated via afferent and efferent fibres of the pudendal nerve relaying in the S2–S4 segments of the sacral cord[5,6]. Dorsogenital nerve stimulation combined with recordings of evoked electrical activity in the pelvic sphincters may thus provide a convenient and reliable means of assessing the innervation of the pelvic floor[7].

The Dantec Neuromatic 2000M equipment (Bristol, UK) was used for all neurophysiological studies, using the amplifier band width 20–2000 Hz.

Dorsogenital nerve stimulation was achieved by placing a bipolar, saline soaked, felt tipped surface electrode (Disa 13L22, Bristol, UK) between the labia minora in contact with the clitoris, with the cathode lying dorsally. Trains of square wave electrical stimuli, 0·2 ms duration, were applied at 2 Hz, the current being gradually increased until the subject felt a sensation of tingling. This procedure was repeated three times and the mean current required to reach the sensory threshold of the dorsogenital nerve was determined.

Electromyographic responses were recorded using a concentric monopolar needle electrode (Disa 13L50) inserted into the superficial

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Table 1 *Urological symptoms and urodynamic findings*

Patient	Age (years)	Number of children	Hysterectomy	Urinary symptoms	Urodynamics
1	54	3	–	Strains to void	Dysynergia bladder neck
2	55	2	–	Frequency	Acontractile bladder
3	66	2	–	Frequency	Prolapsed bladder neck
4	62	2	–	—	Increased bladder capacity
5	37	2	+	—	Increased bladder capacity
6	43	0	+	—	Genuine stress incontinence
7	52	4	+	Incontinence, frequency	Unstable bladder/ Genuine stress incontinence
8	43	2	+	Incontinence, frequency	Genuine stress incontinence
9	41	2	+	Incontinence, frequency	Increased bladder capacity
10	22	0	–	—	Normal
11	48	2	–	—	Normal
12	26	0	–	—	Normal
13	21	1	–	—	Normal
14	24	2	–	—	Normal
15	31	1	–	—	Normal
16	20	0	–	—	Normal

part of the external anal sphincter. In addition, electromyographic responses in the urethral sphincter were recorded using a bipolar platinum ring electrode (Disa 21L11) mounted on a 14 Fr gauge Foley catheter 1·5 cm proximal to the balloon. With the balloon inflated and pulled back against the bladder neck, the electrode lay within the urethral sphincter.

After determining the dorsogenital nerve sensory threshold, trains of up to 100 stimuli were applied at supramaximal level (3 × threshold level), most subjects found this part of the test uncomfortable, but tolerable. Electromyographic responses in both anal and urethral sphincters were processed using a built-in averaging facility, displayed on a storage oscilloscope and recorded on heat sensitive paper.

Latency times of any evoked activity in the anal and urethral sphincters were measured from the stimulus artefact to the take off point of the first detectable response

During the same investigation, motor unit potentials were recorded from the external anal sphincter. Four different needle insertions were used to record a total of 20 individual potentials (each representing a different site within the muscle). The duration, amplitude and number of phasic components of each action potential were assessed, using the 'trigger' and 'delay' facility of the recording equipment.

Videocystometry. Combined filling and voiding cystometrograms were performed with simultaneous radiographic screening. Two Vygon® (Ecouen, France) tubes, 1·2 mm diameter, were passed into the bladder, one tube was used to fill the bladder with 37 per cent Urografin® (Schering Health Care Ltd, Burgess Hill, UK) at room temperature, the other was filled with aqueous chlorhexidine acetate (0·02 per cent) and used to record total bladder pressure. A similar Vygon catheter was used to measure rectal pressure. Both manometric tubes were attached via Statham (California, USA) transducers to a Disa 2100 6-channel urodynamic system and chart recorder. Manometric recordings were reviewed in combination with video recordings of the radiographic images obtained during the study

The bladder was filled at approximately 50 ml/min, bladder function being assessed in accordance with the recommendations of the International Continence Society[8].

Combined anorectal manometry/external and sphincter electromyography. With the subject lying in the left lateral position, pressures were recorded in the rectum and at multiple sites in the anal canal using a multilumen perfused manometric probe (outside diameter 5 mm) that incorporated a rectal balloon[2]. The electrical activity of the external anal sphincter was recorded throughout the study using a bipolar wire electrode[2] inserted into the subcutaneous part of the external anal sphincter via a 23G hypodermic needle (B.D Microlance, Oxford, UK).

After measurement of basal and squeeze pressures[2], the rectal balloon was progressively distended with air in increments of 10 ml, up to a maximum volume of 100 ml, or until the patient found the distension intolerable. Distension was maintained at each volume for 60 s, and was followed by a rest period of at least a further 60 s. The following measurements were made: (1) the threshold distension volume required to initiate anal relaxation; (2) the lowest volume required to prevent recovery of the anal pressure to the preinflation value, (3) the threshold volume required to elicit electromyographic activity in the external anal sphincter; (4) the minimum rectal volume perceived by the subject; (5) the threshold volume required to produce the sensations of flatus and a desire to defaecate Next, subjects were asked to increase their intra-abdominal pressure by inflating a rubber party balloon. The existence of a reflex increase in external anal sphincter electromyographic activity was noted. Finally, the ability of subjects to evacuate two simulated stools of different shape and consistency was tested. A soft, sausage-shaped silicone prosthesis (volume 30 ml; 85 mm × 25 mm × 17·5 mm) simulated a normal stool, while a plastic sphere 18 mm in diameter attached to a metal beaded chain represented a hard pellety stool. Insertion was facilitated using lubricant KY Jelly (Johnson and Johnson Ltd., Slough, UK) and each object was pulled down so that its lower pole was resting against the innermost aspect of the anal sphincter. With the electromyographic electrode *in situ*, subjects were left alone on a commode and instructed to evacuate the simulated stool; the time taken to pass each object was noted

Statistical analysis

Data that appeared to be normally distributed were analysed using an unpaired Student's *t* test; the Mann–Whitney *U* test was applied to non-parametric data. Two-tailed Fisher's exact test and the χ^2 test were used when comparing the proportion of patients and controls who exhibited a particular feature

Results

Neurophysiological tests

Electrical stimulation of the dorsogenital nerve evoked responses from the external anal sphincter in nine of ten healthy controls, and from the urethral sphincter in nine of ten healthy controls. These responses were present in the external anal sphincter in only seven of 16 constipated patients, and in the urethral sphincter in only six of 16 constipated patients ($\chi^2=5\cdot56$ and $6\cdot95$ respectively, $P=0\cdot02$ and $P<0\cdot01$). All normal subjects, but only nine of 16 constipated women, had at least one recordable evoked response ($P<0\cdot05$).

Dorsogenital nerve sensory thresholds were similar in healthy controls and constipated patients. Reflex latency times were also similar in controls and those patients in whom an evoked response was present.

Motor unit potentials were within reported normal limits of duration and amplitude[9,10] in all controls and in 12 of the 13 constipated women tested. Only one patient showed abnormally prolonged polyphasic potentials suggestive of previous denervation.

Urodynamics

Nine (56 per cent) of the constipated women had evidence of concurrent bladder dysfunction[11] (*Table 1*). These included the six patients complaining of urinary tract symptoms, two asymptomatic patients with abnormally high bladder capacities[11]

Table 2 *Anorectal manometry results*

	Patient	Control	*P*
Maximum basal pressure (cmH_2O)	76 (9)	79 (9)	n.s.
Maximum squeeze pressure (cmH_2O)	130 (19)	147 (15)	n.s.
Internal anal sphincter relaxation-threshold (ml)	28 (7)	32 (9)	n.s.
Flatus threshold (ml)	29 (4)	18 (2)	0.02

Values are mean (s.e.m.); n.s., not significant

(1500 ml and 759 ml) associated with a large amount of residual urine and a further patient with genuine stress incontinence. Patients with abnormal urodynamics were significantly older (mean (s.e.m.) 50 (3) years) than those with normal urethrovesical function (mean (s.e.m.) 27 (4) years; $P=0·004$) and had more children (medians 2 *versus* 1, $P=0·04$). The five patients, who had had a previous hysterectomy (*Table 1*), all had urodynamic abnormalities ($P=0·03$, compared with the women who had not had a hysterectomy).

Eight of the nine patients with disordered urethrovesical function had at least one absent evoked sacral reflex; the pudendourethral reflex was unobtainable in six of these eight women. However, four of seven patients with normal urodynamic studies also had an absent pudendourethral reflex.

Combined anal manometry and external anal sphincter electromyography

All patients had evidence of anorectal dysfunction, in that rectal sensation was blunted and most patients were unable to relax the external anal sphincter during defaecation.

The minimum volume of rectal distension that elicited the sensation of flatus (*Table 2*) was significantly higher in constipated women than in normal controls (mean (s.e.m.) 28·7 (3·9) ml *versus* 17·8 (2·2) ml; $P=0·02$) and rectal distension up to a volume of 100 ml failed to initiate a desire to defaecate in 62 per cent of constipated patients, compared with only 5 per cent of healthy subjects ($\chi^2=13·2$, $P<0·0005$).

Although similar proportions of patients and controls successfully evacuated the simulated stools within 5 min, fewer patients were able to relax the external anal sphincter during attempted defaecation (plastic sphere 27 *versus* 88 per cent, $\chi^2=10·81$, $P<0·001$; silicone sausage 36 *versus* 71 per cent, $\chi^2=3·77$, $P=0·05$). Successful defaecation tended to take longer in the constipated group, although this difference did not reach statistical significance.

Basal and squeeze pressures were similar in both constipated and healthy women and there were no significant differences in the rectal volume required to either initiate relaxation of the internal anal sphincter or to elicit a relaxation that was sustained for 60 s (*Table 2*). External anal sphincter electrical responses to rectal distension were seen in 88 per cent of patients and all controls; threshold distension volumes were similar in both groups. External anal sphincter electrical responses to rises in intra-abdominal pressure were also seen in all patients and controls.

The results of combined anorectal manometry and electromyography were no different in the nine patients with an absent pudendoanal reflex compared with the remainder of the constipated women.

Discussion

Our results show that electrical stimulation of the dorsogenital nerve failed to evoke reflex activity in both the external anal sphincter and the urethral sphincter in 75 per cent of chronically constipated women compared with 20 per cent of normal individuals The observation that dorsogenital nerve sensory thresholds were normal and easily recorded in all subjects and motor unit potentials were of normal duration in all but one of the constipated women confirmed the accuracy of our stimulation and recording techniques and indicated integrity of both afferent and efferent limbs of the reflex, even in those patients who had had a hysterectomy. The absence of evoked responses would therefore suggest a localized anatomical or physiological disruption of neural signals transmitted through the sacral cord segments.

A similar conclusion was reached by Varma and Smith[7] who demonstrated prolonged pudendoanal latencies in association with normal sensory thresholds and normal motor unit potentials in 15 chronically constipated women, although complete absence of evoked external anal sphincter activity was noted in only two of their patients. These investigators suggested a conduction defect in the conus medullaris resulting from an occult sacral cord neuropathy, although such a lesion would have to be very localized, as most aspects of sacral cord function were spared. An alternative explanation for these findings is inhibition of the evoked reflexes by efferent signals from higher centres. Indeed, Bradley *et al.*[12] noted that it was possible for subjects to consciously inhibit electrically evoked sacral reflexes, although no subsequent reports have confirmed their experimental findings. Additional evidence which might suggest excessive central modulation of afferent input to the sacral cord is the highly selective nature of the anorectal sensory impairment found in constipated patients[2,3,7,13].

Is the absence of evoked sacral reflex activity a genuine reflection of disordered bladder and anorectal function? Our results appear to indicate that there is little correlation between the neurophysiological findings and disturbances in bladder and anorectal function, as most patients with absent evoked sacral reflexes had normal external anal sphincter electromyographic responses to rectal distension and increases in intra-abdominal pressure. However, as it is claimed that sacral reflex stimulation is a more sensitive method of identifying sacral cord dysfunction than simple electromyographic techniques[6,14,15], this technique may identify minor disturbances in sacral cord integration that do not necessarily manifest themselves as gross disturbances in function.

In conclusion, we have demonstrated that the majority of severely constipated women display abnormalities in the co-ordination of normal urethrovesical and anorectal function and our results suggest that the 'lesion' responsible for these changes lies within the central nervous system. It is possible that the underlying mechanism in these constipated women involves excessive supraspinal inhibition of normal sacral cord function, perhaps via a subconscious learned response, although further work would be necessary to establish this.

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Announcement

USCI, Division of Bard Limited, have announced the launch of the Bard Surgical Scholarship Awards scheme.

The scheme is open to UK based registrars, senior registrars and research fellows, specializing in vascular surgery. Educational travel grants of £3000 (sterling) and £1000 will be awarded to candidates submitting the original research papers judged to be of the highest standard.

Further details and application forms may be obtained from: Surgical Product Manager, Bard Limited, Forest House, Brighton Road, Crawley, West Sussex, RH11 9BP, UK. Telephone number: 0293 27888.

The closing date for entries is 30 September 1989.

Br. J. Surg. 1989, Vol. 76, July, 752–755

Anal endosonography in the evaluation of perianal sepsis and fistula *in ano*

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Anal endosonography has been performed in 22 patients with fistula in ano *and perianal sepsis and compared with the operative findings. Using a special hard cone attachment to a radial 7 MHz probe the examination was well tolerated, rapid and generally accurate, detecting two unsuspected foreign bodies and all seven complicated fistula* in ano *preoperatively.*

Keywords: Imaging, anus, ultrasound

Surgery for fistula *in ano* is potentially difficult, and prior knowledge of a complicated fistula might be beneficial[1]. A complicated fistula has been defined as a fistula other than a superficial or simple intersphincteric fistula[2]. Clinical examination will identify an external opening and sometimes an internal opening. Subcutaneous induration and induration within the anal canal suggest possible sepsis and the direction of a track. However the exact anatomy is often difficult to determine. Probing a track may help but this is painful in the conscious patient and potentially dangerous[3].

Radiological delineation of fistulous tracks with water soluble contrast media has been described[4], but is considered of limited value[5]. Anal endosonography has the potential to image pathological abnormalities in the anal canal and perianal region. Pararectal abscesses and fistulae have been identified with a 5 MHz probe[6]. We have used a higher frequency 7 MHz probe, which provides greater near-field resolution, initially to establish the normal ultrasound anatomy of the anal canal and then to discover what features of fistula *in ano* can be visualized, so as to determine whether or not endosonography has a role in preoperative assessment.

Patients and methods

Twenty-two consecutive patients admitted to St. Mark's Hospital with a diagnosis of recurrent perianal sepsis or fistula *in ano* were studied prospectively. After clinical assessment, endosonography was performed by P.J.L. or C.I.B., without knowledge of the clinical findings. No bowel preparation was required. A Brüel and Kjær (UK) Ltd., Harrow, UK ultrasound scanner type 1846, with a 7 MHz rotating endoprobe, of 3-cm focal length was used. A specially designed hard sonolucent plastic cone, of maximum diameter 2 cm, was filled with degassed water to provide protection for the rotating probe and effective acoustic coupling in the anal canal (*Figure 1*). The lubricated cone was inserted with the patient in the left lateral position and serial images obtained on slow withdrawal.

Surgery was performed the following day by one of the consultant staff without prior knowledge of the sonographic findings.

The fistulae were classified by internal openings, muscle defects, scars, abscesses, either superficial, intersphincteric, supralevator or extralevator, and tracks with or without a horseshoe configuration. These criteria were used to compare the findings on endosonography and at surgery.

Results

Patients tolerated the procedure well with the exception of one patient with a Crohn's stricture at the anorectal junction.

The sonographic anatomy of the normal anal canal is shown in *Figure 2*. This was derived from the known anatomy of the rectum, correlation of surgical findings in other cases and some experimentation. The location of the external anal sphincter was confirmed at endosonography by identifying an electrode inserted into the muscle during electromyophysiological studies, and the intersphincteric plane by observing water injected into this space in an operative specimen.

The smooth muscle of the internal anal sphincter was clearly identifiable as a homogeneous hypoechoic band extending caudally to below the level of the anal valves, and lying in the same plane as the muscularis propria of the rectum. Striated muscle had a different acoustic texture and the external sphincter could be traced posterolaterally from the levator muscle down to the subcutaneous level as a broad band of mixed echogenicity with a prominent linear component. In male patients the external sphincter tapered anteriorly into two arcs that met in the midline, but in female patients the muscle was relatively deficient anteriorly adjacent to the vagina and perineal body. The internal sphincter was separated from the external sphincter by a narrow hyperechoic band of the intersphincteric plane. Directly in contact with the cone was the hypoechoic layer of mucosa. Between this and the internal

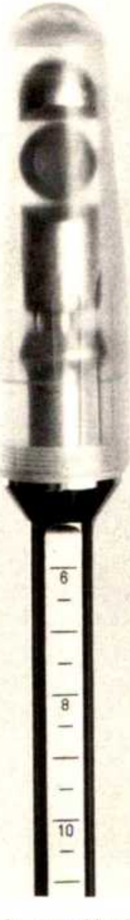

Figure 1 *Anal endosonography assembly showing the hard plastic cone (maximum diameter 2 cm) covering the rotating 7 MHz probe*

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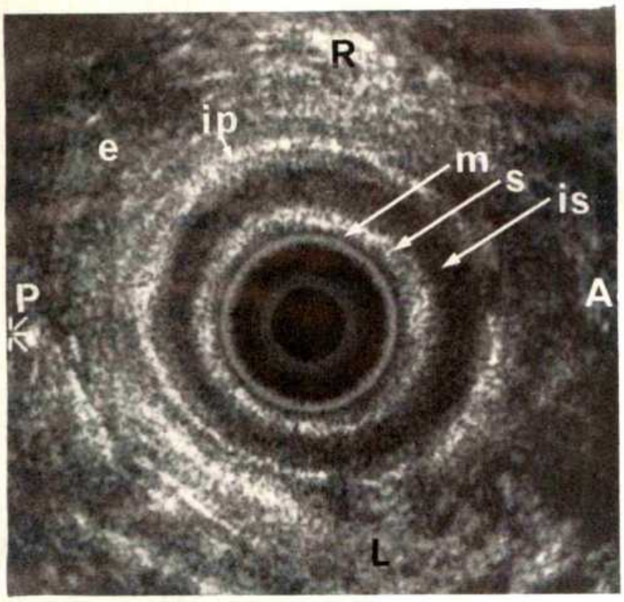

Figure 2 *Anal endosonography in upper anal canal showing orientation of images (P, posterior; A, anterior; R, right lateral; L, left lateral) and normal anatomy (m, mucosa; s, submucosa; is, internal sphincter; ip, intersphincteric plane; e, external sphincter)*

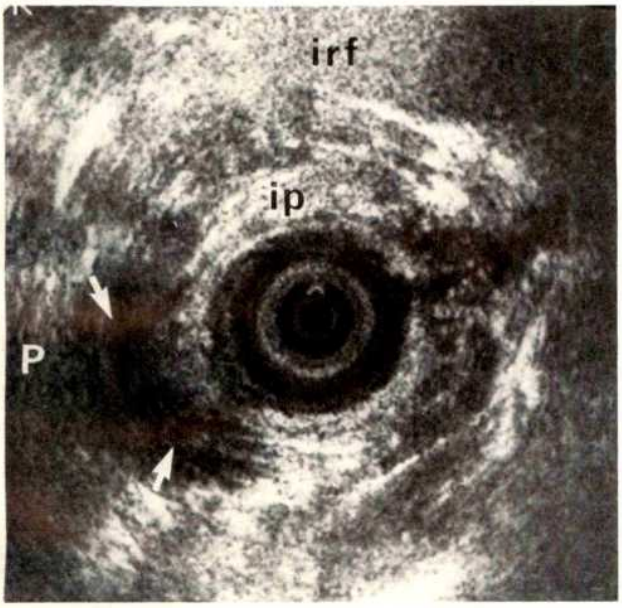

Figure 3 *Anal endosonography showing posterior abscess (arrows) with distortion of the adjacent external sphincter. Increased echoes seen in the ischiorectal fossa (irf). Note the widening of the intersphincteric plane (ip)*

sphincter was the echogenic submucosa, which became progressively denser and thicker caudally. Laterally at the edge of the field of view and deep to the external sphincter, bright echoes could be seen from reflections in the ischiorectal fossa (*Figure 3*).

Internal openings were visible as a break in the mucosal layer, with the site and level estimated from the position of the probe. Defects in the internal sphincter, caused either by previous surgery or sepsis, appeared as a loss in continuity in the circumferential ring of muscle. Infection within the intersphincteric plane caused widening and distortion of an otherwise narrow plane (*Figures 3* and *4*). Scars produced a homogeneous hypoechoic area, usually with a regular outline. Abscesses, although of similar hypoechogenicity were less homogeneous, containing areas of mixed echogenicity and more irregular in outline. Tracks created hypoechoic bands within the intersphincteric plane, and usually communicated with a cavity or scar. Tracks sometimes extended around the anal canal in a 'horseshoe' configuration (*Figure 5*).

Abnormalities of the external sphincter were difficult to define as associated changes in the intersphincteric plane altered the echo pattern of the adjacent muscle (*Figure 3*). Hypoechoic defects within the ring of striated muscle were interpreted as trans-sphincteric extension of inflammatory changes; this was supported by the surgical findings. The ischiorectal fossa was poorly defined, so that supralevator extension of such an abscess was difficult to recognize.

The surgical findings revealed a chronic abscess in 16 patients (two superficial, ten intersphincteric, two infralevator and two supralevator). A fistulous track was present in 12 (seven intersphincteric, five trans-sphincteric) and a horseshoe shaped track in four. Altogether seven of the fistulae were classified as complex.

The correlation between endosonography and surgical findings is shown in *Figure 6*. Endosonography identified the

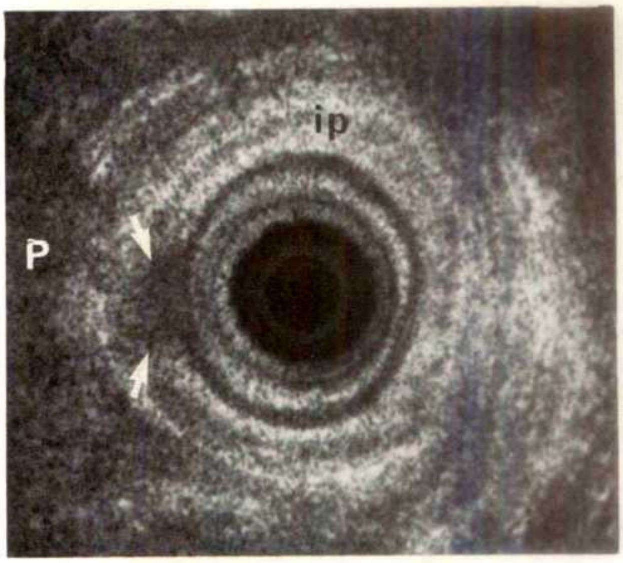

Figure 4 *Anal endosonography at level of anal valves demonstrating a posterior intersphincteric abscess (arrows) and adjacent muscle defect in the internal sphincter. Note also widening of the intersphincteric plane (ip)*

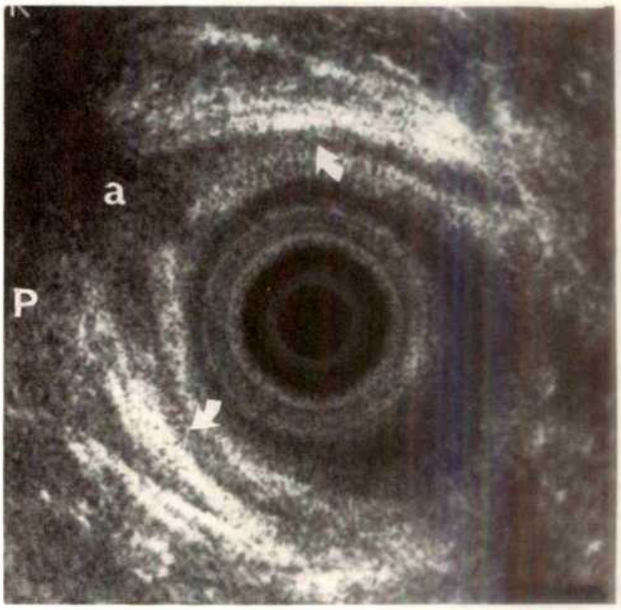

Figure 5 *Anal endosonography showing a posterior intersphincteric abscess (a), with an intersphincteric horseshoe track (arrows)*

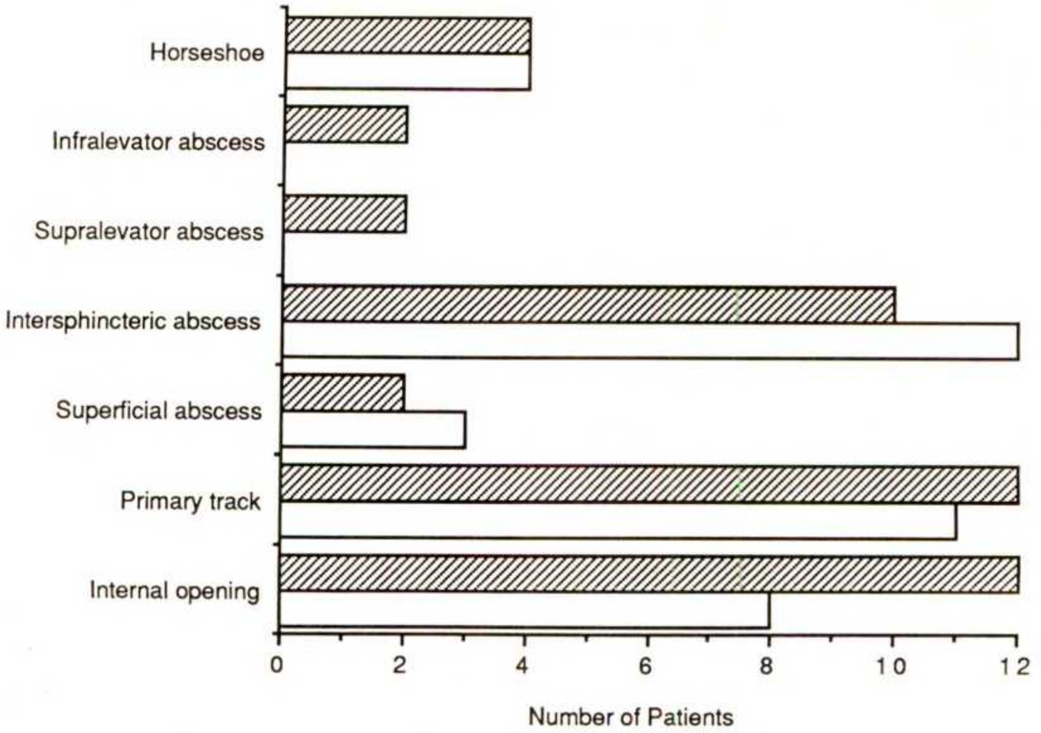

Figure 6 *Correlation between endosonographic and surgical findings in 22 patients with fistula* in ano; □, *ultrasound;* ▨, *surgery*

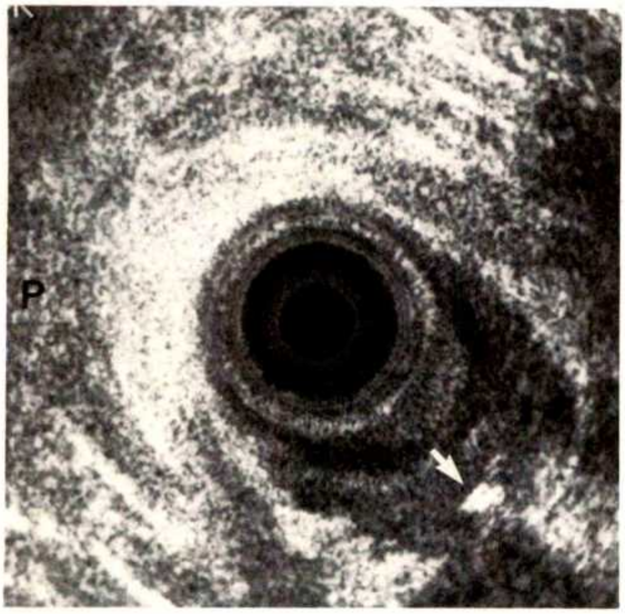

Figure 7 *Anal endosonography showing a bright focal lesion which proved to be a retained seton suture (arrow) within an anterolateral abscess cavity*

majority of the pathological changes except for infralevator and supralevator abscesses. The two patients incorrectly diagnosed as having intersphincteric abscesses, were found at surgery to have supralevator extensions not recognized by endosonography. In three patients small highly discrete echogenic foci were found and diagnosed as foreign bodies. Two of these were confirmed as such: one was a grape seed in an intersphincteric abscess and the other a buried seton suture (*Figure 7*). The third patient had a partially epithelialized track. Two superficial perianal abscesses were correctly diagnosed. The third proved to be a chronic Bartholin's abscess.

All of the seven patients with surgically proved complicated fistulae were correctly identified preoperatively.

Discussion

The sonographic anatomy of the normal rectum has been investigated extensively in relation to determining the depth of tumour invasion[7–10]. Five basic ultrasound layers have been described in the rectum. There are two hyperechoic layers consisting of the submucosa and serosa, interleaved with three hypoechoic layers of the mucosa, muscularis mucosa and muscularis propria. Some investigations of anal canal anatomy have been undertaken with 4 or 5 MHz transrectal probes in fistulae[6] and anal cancer[11], which support our description of the internal anal sphincter. Our understanding of the endosonographic anatomy has been built up from experience in rectal endosonography, extrapolation of the known appearances of various layers, correlation with pathological findings and some experimentation. The validity of the description offered is supported by complete agreement between the anatomical location of abnormalities predicted and the findings at surgery.

Two aspects of the apparatus were found to be critical for accurate examination of the anal canal. The 7 MHz probe has considerably improved resolution in the near field, and was essential to show subtle changes. The hard cone has been designed specifically for use in the anal canal. Endosonography was attempted with the standard rectal balloon, but the rotating probe tended to catch and tear the balloon as it was manipulated in the anal canal. To avoid this, it was necessary to fill the balloon with large volumes of water forcibly to dilate the anal canal, which caused anatomical distortion and discomfort. The hard cone is no more traumatic than digital examination, and keeps the canal open with its walls parallel for true anatomical presentation.

Supralevator extension of an abscess and disease within the ischiorectal fossa were not identified endosonographically as image definition in this area was poor. There are perhaps two reasons for this. Ultrasound requires acoustic coupling to obtain any picture and, as the probe gives a radial field, only the immediate structures within a radial plane along the canal will be imaged with the hard cone attachment. Some improvement may be possible by using the balloon attachment designed for rectal examination, as the balloon would maintain acoustic contact in the ampulla to reveal any lesion in this plane. Another problem is lack of penetration of the ultrasound beam. Lesions lying deep to the external sphincter may be outside the field of view.

Identification of internal openings was not wholly successful, possibly because of the proximity of the mucosa to the probe, so that it was not within focal range. Although fistulae with a high internal opening have been defined as being complicated[12], most openings occur at the level of the anal valves regardless of complexity. Intersphincteric disease and trans-sphincteric tracks were correctly identified in most patients. Differentiation between abscess cavities, granulated tracks and scars was sometimes difficult but has improved with experience. Straight tracks were easily identified, but smaller and oblique tracks were more difficult to image. There was good correlation between endosonography and surgery in identifying horseshoe extensions and in detecting foreign bodies.

Endosonography requires experience, but is a simple technique that is inexpensive and well tolerated by the patient. In this study, all seven of the fistulae considered to be complex at surgery were identified preoperatively. Such knowledge may influence operative technique and would be of particular help to those with limited experience in this field of surgery.

Acknowledgements

The authors wish to express their thanks to Brüel and Kjær (UK) Ltd. for the loan of the hard cone water bath, the ICRF Colorectal Cancer Unit at St. Mark's Hospital for the use of the ultrasound equipment, and the surgeons of St. Mark's Hospital for allowing us to study their patients. P.J.L. is supported by the St. Mark's Research Foundation.

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Effect of mechanical bowel preparation on anastomotic integrity following low anterior resection in dogs

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To assess the effect of mechanical bowel preparation on anastomotic integrity after low anterior resection, 36 mongrel dogs were randomized to have low anterior resection with or without mechanical bowel preparation. All dogs received prophylactic antibiotics and anastomotic integrity was assessed on the ninth postoperative day by barium enema, inspection of anastomoses for defects after careful excision at laparotomy, and anastomotic bursting pressures. Bursting pressures were significantly higher ($P<0{\cdot}005$) *in the group with bowel preparation. Anastomotic defects were present in 13 per cent of animals with bowel preparation and 47 per cent without bowel preparation* ($P=0{\cdot}057$)*. Pelvic abscess and death from peritonitis occurred in 6 per cent of the group with bowel preparation and 29 per cent of the unprepared group. Mechanical bowel preparation significantly enhanced anastomotic integrity and reduced complications in this model.*

Keywords: Rectum, surgery, surgical technique, animal experiment

A recent study by Irving and Scrimgeour has questioned the need for mechanical bowel preparation when performing colorectal resection with primary anastomosis[1]. In a series of 72 consecutive colectomies with primary anastomosis where all preoperative and perioperative mechanical preparation was omitted and the patients were treated by a single peroperative intravenous dose of cefuroxime and metronidazole, the authors reported a clinically apparent anastomotic dehiscence rate of zero, a wound infection rate of 8·3 per cent, and an operative mortality rate of 2·7 per cent. However, only seven patients in the series had elective low anterior resections, the area in large bowel surgery in which anastomotic dehiscence is most commonly observed. Goligher and associates reported anastomotic dehiscence in 18 of 26 patients (69 per cent) submitted to low anterior resection when dehiscence was sought by digital and sigmoidoscopic examination[2]. Seven of these patients, one of whom died, had overt faecal fistulae discharging on to the abdominal wall or into the vagina.

The aim of the present study was to examine the effect of mechanical bowel preparation on anastomotic integrity following low anterior resection in dogs.

Materials and methods

Animals

Thirty-six mongrel dogs were randomized to two groups: one with and one without bowel preparation. The average weight and male:female ratio in both groups were similar. All were fed Febo® (Quaker Latz, Euskirchen, FRG) dog food and had water *ad libitum*. Dogs were fasted from midnight on the day of the operation and the bowel preparation group had fluids only for 48 h preoperatively. Twenty-four hours preoperatively, animals in the bowel preparation group were given sodium picosulphate 10 mg, magnesium oxide 3·5 mg and citric acid 12 g (Picolax®, Nordic Pharmaceuticals Ltd., Feltham, UK) orally as a single dose. Postoperatively all animals were given water only for 24 h and full diet as tolerated thereafter.

Animal model

Dogs were anaesthetized with sodium thiopentone (5 mg/kg), intubated with a cuffed endotracheal tube and ventilated with nitrous oxide, halothane and oxygen. The bowel preparation group had on-table water enemas using a cuffed polyethylene tube passed per rectum in a closed system until clear. All dogs received a single dose of prophylactic antibiotics (cefuroxime 250 mg and metronidazole 250 mg, intravenously) at induction of anaesthesia. Abdomens were shaved and prepared with Betadine® (Napp Laboratories Ltd., Cambridge, UK). Laparotomies were carried out through a midline incision. The left colon and rectum were mobilized and a segment of bowel from the caudal mesenteric artery (inferior mesenteric) to mid-rectum was excised (*Figure 1*). Bowel ends were cleaned with chlorhexidine swabs and a tension free anastomosis performed using an inverting, single-layered technique with interrupted 2/0 Nurolon® (Ethicon Ltd., Edinburgh, UK)[3]. Laparotomy incisions were closed with 1/0 continuous nylon and skin with 3/0 nylon. No drains were used. All operations were carried out by the same surgeon and assistant. All animals received 1 litre of normal saline intravenously at operation.

Assessment of anastomotic integrity

All animals were killed on the ninth postoperative day by overdose with pentobarbitone sodium (60 mg/kg), and anastomotic integrity was assessed by single contrast barium enema, inspection of anastomoses for defects after careful excision at laparotomy, and anastomotic bursting pressures. Bursting pressures were carried out on a standard length of bowel after the faecal content had been milked out and perianastomotic tissue adherent to the anastomosis removed. The proximal end of the anastomosis was connected to an air-injecting perfusor and air was perfused at a constant rate by means of a polyethylene tube. The distal end was connected to a 0–300 mmHg pressure transducer and the pressures were recorded. The bowel was inflated under water and the point at which air bubbles appeared from the anastomosis taken as the bursting pressure.

Statistical analysis

Comparison of anastomotic dehiscence rates in both groups on barium enema, and inspection, was made by Fisher's exact test. Comparison of bursting pressures in both groups was made by the Mann–Whitney *U* test.

Results

In three of the 36 dogs anastomotic integrity was not evaluated because the animals died in the perioperative period. One was a preoperative death secondary to aspiration pneumonia which occurred when the animal was receiving Picolax. The other two were postoperative deaths: a death due to anaesthesia and a death due to dehiscence of the laparotomy incision on the third postoperative day. The anastomosis in the latter was clinically intact. Thus 33 dogs were evaluable, 17 without and 16 with bowel preparation.

Four dogs (23 per cent) with no bowel preparation and one (6 per cent) with bowel preparation had anastomotic defects

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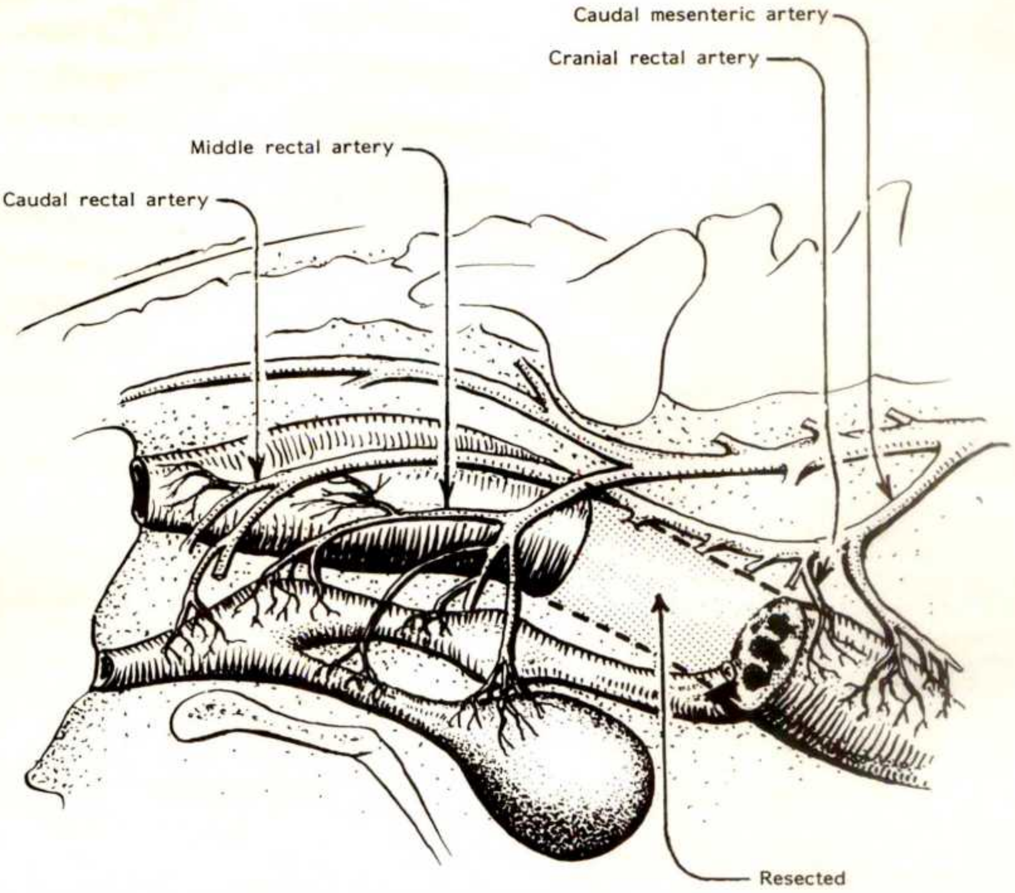

Figure 1 *Lateral view of the rectum and anal canal of a dog indicating extent of bowel resection*

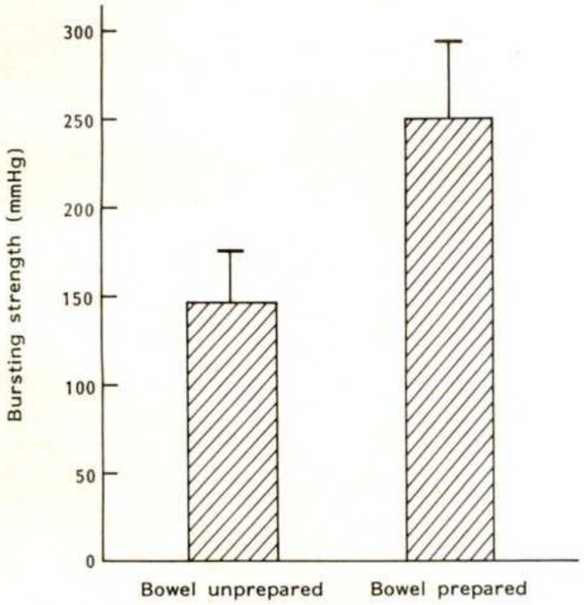

Figure 2 *Anastomotic bursting pressures in both groups (pressures were measured on all anastomoses)*

on barium enema (P = n.s.). Eight (47 per cent) without and two (13 per cent) with preparation had anastomotic defects on inspection of anastomoses after their removal from the peritoneal cavity at laparotomy ($P = 0.057$). No anastomosis was damaged while performing this procedure. Anastomotic bursting pressures were significantly higher ($P < 0.005$) in the group with bowel preparation (*Figure 2*).

There were two deaths secondary to peritonitis and three pelvic abscesses in the unprepared group. There was one death secondary to peritonitis in the prepared group. All deaths and abscesses were associated with anastomotic dehiscence. Cultures from abscesses and peritoneal fluid confirmed colonic microflora in all cases.

The extent of faecal load in the colon at the time of operation was assessed for each unprepared dog. This was graded clinically in increasing amount from +1 to +4 (*Table 1*). While there was no significant correlation between anastomotic dehiscence and faecal load both animals that died had +4 faecal load at the time of operation. Faecal load was minimal (+1) in all 16 prepared dogs.

The effect of contamination (macroscopic spillage) at operation on anastomotic dehiscence and complications was

Table 1 *Effect of faecal load on anastomotic dehiscence and complications in the 17 dogs with no bowel preparation*

Faecal load	Number	Anastomotic dehiscence	Pelvic abscess	Deaths
+	3	2	2	—
++	5	1	—	—
+++	4	2	1	—
++++	5	3	—	2

Table 2 *Effect of contamination at operation on anastomotic dehiscence and complications*

Group	Number	Anastomotic dehiscence	Pelvic abscess	Deaths
Bowel prepared	7 (44)	1	0	1
Bowel unprepared	3 (18)	3	1	1

Values in parentheses are percentages calculated from the total number of dogs in each group also assessed (*Table 2*). This occurred more commonly in the prepared group but was less likely to be associated with anastomotic dehiscence: 14 per cent compared with 100 per cent in the unprepared group (P=n.s.).

Discussion

Mechanical bowel preparation was shown to increase anastomotic bursting pressures significantly and reduce anastomotic dehiscence rates and related complications after low anterior resection in mongrel dogs. The model of low anterior resection in dogs is analogous to that of low anterior resection in man in many respects. The microflora of the large intestine in both are similar and experimental intra-abdominal sepsis using intestinal microflora in dogs is almost completely prevented by use of a cephalosporin or metronidazole[4]. The blood supply and anatomical relationships of the rectum and sigmoid are also similar in the dog and man[5].

The rate of anastomotic dehiscence after colorectal resection with primary anastomosis varies widely among reported series[1,6–8]. It is significantly higher after anterior resection of the rectum compared with intraperitoneal enteric anastomoses[6] and higher again when low anterior resection is compared with high anterior resection[2]. There are many causes of anastomotic dehiscence. However, in the Large Bowel Cancer Project[6], a prospective study looking at dehiscence rates in almost 1500 patients undergoing colorectal resection with primary anastomosis, the most important significant factor was the variability in dehiscence rates among different surgeons.

There are few data available in the literature on the effect of mechanical bowel preparation on anastomotic dehiscence. Hughes, in a study of 46 patients who underwent bowel preparation and 51 who did not, found no difference in wound infection rates, peritonitis or deaths between the groups in a personal selected series[9]. Goligher and associates, examining the influence of gross faecal loading on anastomotic dehiscence after both low and high anterior resection, showed a higher incidence of dehiscence in patients with colonic loading[2]. This difference, however, was not quite statistically significant and the patients with gross faecal loading were chosen from a group in which mechanical bowel preparation had failed.

The mechanism of increased anastomotic dehiscence and reduced bursting strengths associated with omission of bowel preparation in this study is difficult to explain. It is noteworthy that the three animals in the unprepared group with faecal contamination all had anastomotic defects. It is well established in experimental studies that intraperitoneal sepsis or placement of faeces at or near an anastomosis increases anastomotic dehiscence rates[10]. Similarly in clinical studies faecal soiling at operation is associated with an increased incidence of anastomotic dehiscence[2,7,11]. Infection causes a reduction in collagen at the anastomosis[10]. This may result from excessive collagenase production or from imbalance between collagenase and controlling tissue inhibitors[12].

Mechanical bowel preparation is shown to enhance anastomotic integrity significantly after low anterior resection. While these data cannot be extrapolated directly to low anterior resection in humans it would seem prudent to continue using bowel preparation in this situation while awaiting results from further clinical and experimental studies on this subject.

Acknowledgements

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Clinicopathologic study of early stage esophageal carcinoma

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*As part of a consecutive series of 370 patients who underwent subtotal esophagectomy because of carcinoma of the thoracic area of the esophagus, between January 1965 and July 1988, in the Second Department of Surgery, Kyushu University Hospital, 42 patients (11.4%) with early stage esophageal carcinomas confined to the intraepithelium, mucosa, or submucosa were studied clinicopathologically. Of these 42, 26 (61.9%) had symptoms; slight dysphagia or chest discomfort was the most common symptom. The remaining 16 (38.1%) had no subjective symptoms. Endoscopic examination proved to be more useful than barium studies. Lugol-combined endoscopy was most effective in detecting the presence and spread of small malignant lesions of the esophagus. At the time of surgery, six patients with submucosal carcinoma of the esophagus had lymph node metastasis, and five died of recurrence. Described herein are the diagnostic features, clinicopathologic characteristics, and long-term results of these 42 patients with early stage, and 328 patients with advanced, carcinomas of the esophagus, detected and surgically treated in our clinics. (*SURGERY *1989;105:706-10.)*

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AS ESOPHAGEAL CANCER rapidly metastasizes to other organs through hematologic and lymphatic routes, early treatment, including surgery and irradiation, has to be given. In Japan, approximately 40% of gastric cancers may be detected in the early stage, when the carcinoma is confined to the mucosa or submucosa.[1, 2] Only 2.5% (7/277) of resected esophageal carcinomas, however, were early stage cancers.[3] Between January 1965 and July 1988, 370 patients with carcinoma of the thoracic part of the esophagus underwent subtotal esophagectomy in the Second Department of Surgery, Kyushu University Hospital. Of these, 328 (88.6%) had advanced cancer and 42 (11.4%) early stage esophageal carcinomas; that is, the depth of cancer invasion was confined to the epithelium, the lamina muscularis mucosae, or to the submucosa. Feasible approaches to early detection, the clinicopathologic characteristics, and the long-term results of these 42 early stage esophageal carcinomas are discussed.

PATIENTS AND METHODS

Between January 1965 and July 1988, 587 Japanese patients with carcinoma of the thoracic esophagus were admitted to the Second Department of Surgery of Kyushu University Hospital. Of these, 370 each underwent subtotal esophagectomy, the rate of resectability being 63.0%. In most patients a one-stage operation was performed: subtotal esophagectomy and dissection of the lymph nodes were carried out via right thoracotomy; the esophagus was reconstructed with a gastric tube via the antesternal route.[4]

Of these 370 patients, 42 (11.4%) had early-stage carcinoma confined to the intraepithelium, mucosa, or submucosa (Table I) that fell under a category of Tis and T1 by new TNM classification.[5] The other 328 (88.6%) had advanced esophageal cancer.

All the resected specimens, including the lymph nodes, were histopathologically examined, and the early and advanced-stage cancers were compared as to their characteristics, mortality rates, and postoperative complications.

The survival rates were estimated with use of the method of Kaplan and Meier,[6] and other statistical analyses were performed with the χ^2 test.

RESULTS

Efficacy of Lugol-combined endoscopy in detecting early stage esophageal carcinoma. Between 1965 and 1984, only 19 of the 270 (7.0%) surgically treated patients had early stage cancers. In all early stage carcinomas detected before 1985, the depth of invasion was limited to the submucosa.

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Table I. Patients

	Early stage carcinoma n = 42 (%)	*Advanced carcinoma n = 328 (%)*
Sex		
Male	35 (83.3)	277 (84.5)
Female	7 (16.7)	51 (15.5)
Pathology		
Well-diff sq ca	6 (14.3)	79 (24.1)
Mod-diff sq ca	24 (57.1)	152 (46.3)
Poorly diff sq ca	12 (28.6)	89 (27.1)
Adenocarcinoma	0	8 (2.4)
Vessel invasion		
Positive	15 (35.7)	207 (63.1)
Negative	27 (64.3)	121 (36.9)
Lymph node involvement		
Positive	6 (14.3)	191 (58.2)
Negative	36 (85.7)	137 (41.8)

Legend: sq ca, Squamous cell carcinoma.

Since 1985, we have used Lugol-combined endoscopy,[7-9] with a remarkable increase in detection of the cancer at an early stage. From January 1985 to July 1988 surgery was done on 100 patients with esophageal cancer, and of these, 23 (23%) had an early stage cancer. In patients seen during these years, if there were doubts about the integrity of the mucosal surface, we instilled about 20 ml of 2% Lugol's solution via a polyethylene tube, under direct vision, and biopsy specimens were taken from the unstained area. In none of the 270 patients treated in the 20-year period from 1965 to 1984 was detection made at the stage at which cancer invasion was limited to the epithelium or the lamina muscularis mucosae. Lugol-combined endoscopy made feasible detection of esophageal cancer at the stage at which it was still confined to the epithelium (1/100, 1.0%) or the lamina muscularis mucosae (6/100, 6.0%). The detection rate of esophageal cancer limited to the submucosa also increased, compared with the earlier periods: 16 of 100 (16.0%) of the patients surgically treated between January 1985 and July 1988 had cancer limited to the submucosa.

Macroscopic classification and location of early stage esophageal carcinoma. The gross appearance of the 42 early stage cancers was macroscopically classified into three types (Fig. 1): elevated, superficial, or depressed. As shown in Table II, all of the cancers limited to the epithelium or lamina muscularis mucosae were of the superficial type. On the other hand, in patients with submucosal cancer there were 15 patients with elevated, 10 patients with superficial, and 10 patients with the depressed types, respectively.

Table II. Macroscopic classification of early stage esophageal carcinoma

	Depth of invasion			
Type	*ep*	*mm*	*sm*	*Total (%)*
I (Elevated)	0	0	15	15 (35.7)
II (Superficial)	1	6	10	17 (40.5)
III (Depressed)	0	0	10	10 (23.8)
Total	1	6	35	42 (100)

Legend: ep, Invasion limited to the epithelium; mm, invasion confined to the lamina muscularis mucosae; sm, invasion confined to submucosa.

Of the 42 early stage esophageal cancers, the majority (26, 61.9%) were located in the middle third of the esophagus; in 2 (4.8%) and in 14 (33.3%) the upper third and lower third of the esophagus were involved, respectively.

Symptoms of early stage esophageal carcinoma. Of the 42 patients with early stage esophageal carcinoma, seven had cancer confined to the epithelium or lamina muscularis mucosae. None of these seven arrived with subjective symptoms. On the other hand, of 35 patients with submucosal carcinoma, 26 (74.3%) had subjective symptoms, such as slight dysphagia (13 patients), chest discomfort (11 patients), or pyrosis (2 patients). In 6 of the 16 patients with no symptoms, early stage esophageal carcinoma was detected at the time of endoscopic follow-up for gastric ulcer. In the other 10 patients with no symptoms, esophageal carcinoma was detected at the time of endoscopic screening for gastric cancer. Of 328 patients with advanced carcinoma, only three (0.9%) had no symptoms. The upper gastrointestinal series revealed esophageal carcinoma.

Although 23 of the 35 submucosal carcinomas were initially diagnosed by means of an upper gastrointestinal series, this type of examination did not lead to detection of mucosal or intraepithelial esophageal carcinoma. At that level of invasion, the carcinomas were initially diagnosed by means of Lugol-combined endoscopy and biopsy; the subsequent upper gastrointestinal series did not lead to an accurate diagnosis.

Results of histopathologic examination. Of the 42 early stage esophageal carcinomas, 6 (14.3%), 24 (57.1%), and 12 (28.6%) were well-, moderately, and poorly differentiated squamous cell carcinomas, respectively. There was no evidence of lymph node metastasis in the seven patients with intraepithelial or mucosal carcinoma, and all malignant tissue was thought to have been completely excised. Among the 35 patients with submucosal carcinoma, however, 15 (42.9%) manifested vessel invasion, and in six (17.1%) there

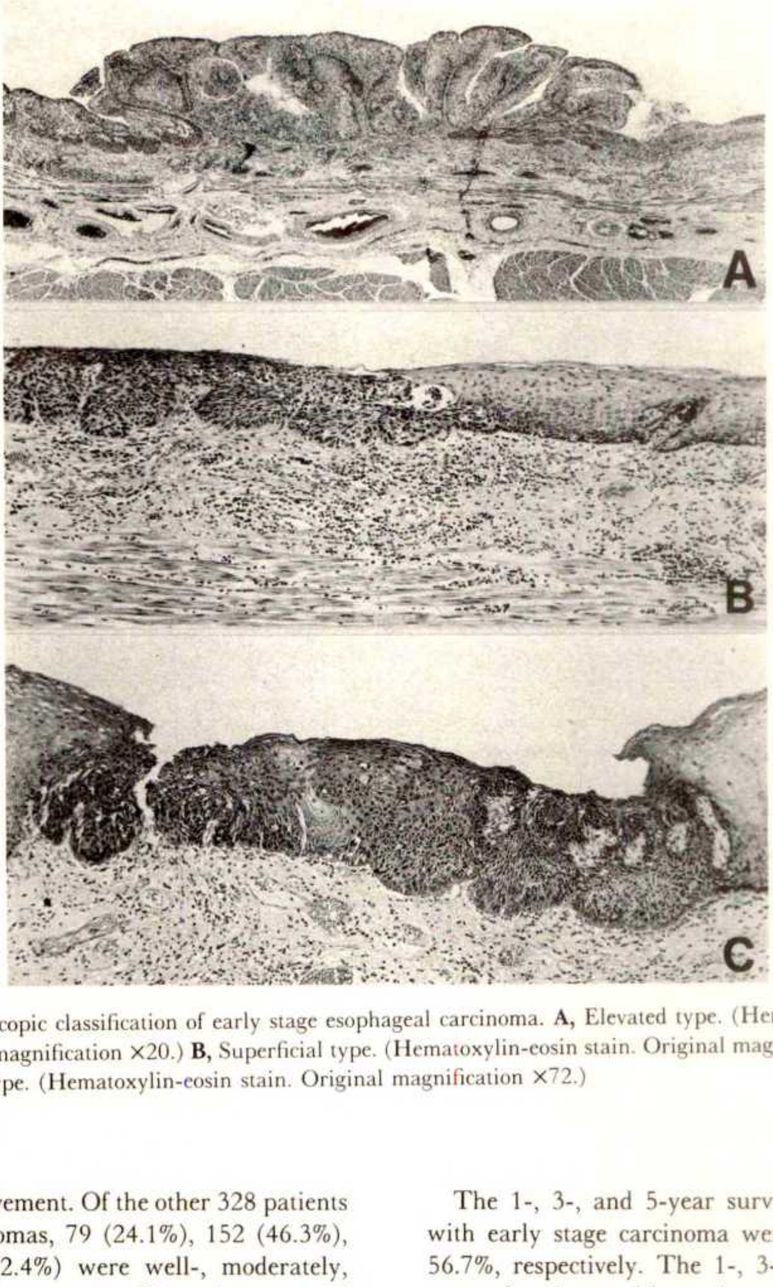

Fig. 1. Macroscopic classification of early stage esophageal carcinoma. **A,** Elevated type. (Hematoxylin-eosin stain. Original magnification ×20.) **B,** Superficial type. (Hematoxylin-eosin stain. Original magnification ×72.) **C,** Depressed type. (Hematoxylin-eosin stain. Original magnification ×72.)

was lymph node involvement. Of the other 328 patients with advanced carcinomas, 79 (24.1%), 152 (46.3%), 89 (27.1%), and 8 (2.4%) were well-, moderately, poorly differentiated squamous cell carcinomas, and adenocarcinoma, respectively.

Outcome. The surgical mortality rates (death within 30 days of surgery) of patients with early esophageal carcinoma and patients with advanced cancer were 2.4% and 5.2%, respectively. Of the latter group, 8 died of pneumonia, 4 of anastomotic leakage, and 2 of heart failure (Table III). All of these deaths occurred in patients surgically treated before 1983; since then, the operative mortality has been nil, mainly because of improvements in nutritional support (intravenous hyperalimentation) and improved respiratory and circulatory care.

The 1-, 3-, and 5-year survival rates for patients with early stage carcinoma were 91.3%, 56.7%, and 56.7%, respectively. The 1-, 3-, and 5-year survival rates of patients with carcinoma invading the proper muscle layer or deeper were 52.9%, 23.0%, and 15.6%, respectively (Fig 2). Thus, prognosis of patients with early stage carcinoma was superior to those with advanced carcinoma, with a statistically significant difference ($p < 0.01$).

In this study there were six patients with early stage carcinomas, yet lymph node involvement was evident at the time of surgery. Of these six patients, five died of recurrence. For 25 patients with no lymph node involvement or vessel invasion, the 5-year survival rate was 79.2%. On the other hand, the 5-year survival rate was only 24.7% for 17 patients with either or both

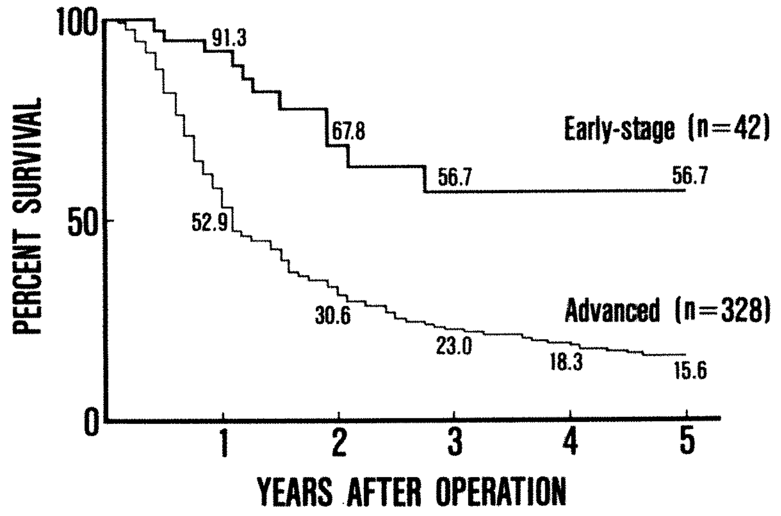

Fig. 2. Actuarial survival rates of surgically treated patients with early stage and advanced esophageal carcinoma. The difference between the two groups is statistically significant ($p < 0.01$).

Table III. Mortality and postoperative complications

	Early stage carcinoma *n = 42 (%)*	*Advanced carcinoma* *n = 328 (%)*	
Mortality	1 (2.4)	17 (5.2)	
(Death within 30 days after surgery)	Pneumonia 1	Pneumonia	8
		Anastomotic leakage	4
		Heart failure	2
		Liver failure	1
		Peritonitis	1
		Cerebral thrombosis	1
Postoperative complications			
Lung	6 (14.3)	83 (25.3)	
Liver	2 (4.8)	25 (7.6)	
Heart	1 (2.4)	5 (1.5)	
Kidney	0	3 (0.9)	
Anastomotic leakage	7 (16.7)	52 (15.9)	
Others	5 (11.9)	29 (8.8)	

factors. The 5-year survival rates for patients with advanced cancer with and without these factors were 12.7% (264 cases) and 27.8% (64 cases), respectively. The survival of patients with early cancer and lymph node involvement and/or vessel invasion was about the same as that of those with advanced cancer without lymph node involvement. Thus, the prognosis of patients with early stage carcinoma with vessel invasion and/or lymph node involvement is far from satisfactory.

DISCUSSION

Matthews et al.[10] reported that in Western countries the overall 5-year survival rate of 4680 patients with esophageal carcinoma treated with current methods was a disappointing 5%. Hence, early detection and adequate treatment require intensive research.

Since 1985, we have made use of Lugol-combined endoscopy, apparently first described by Brodmerkel in 1971. Application of this Shiller's test led to a marked increase in the early detection of esophageal carcinoma, when the invasion was confined to the intraepithelial, mucosal, or submucosal layer. Carcinomatous lesions contain no glycogen and thus remain unstained. The extent of the lesion may easily be determined, even by gross inspection.[7,9] Of the 270 patients we surgically treated between 1965 and 1984, a malignancy at the stage of intraepithelial or mucosal invasion was not detected. Since we began to use Shiller's test, however, we detected cancers limited to the epithelium in 1 of 100 patients treated during that period, and six patients were treated before the invasion had gone beyond the lamina muscularis mucosae. Therefore Lugol-combined endoscopy and endoscopic biopsy are indeed effective diagnostic tools available for the detection of small cancers of the esophagus. None of these lesions was evident on x-ray films.

Koehler et al.[11] defined early esophageal carcinoma as tumors 3.5 cm or less in length that involve only one wall of the esophagus, as viewed radiographically. The Japanese Society for Esophageal Disease defines superficial esophageal carcinoma as lesions in which infiltration does not go beyond the submucosal layer,[12] a definition based on postoperative pathologic findings. In our series of 370 patients who underwent surgical therapy for esophageal cancer, 42 (11.4%) were thus classified as cases of superficial esophageal carcinoma, or as Tis and T1 carcinoma, according to the new TNM classification.[5]

The operative mortality of patients undergoing esophageal surgery by a specialist trained to do this surgery now stands at less than 7%.[13, 14] Factors that reduce postoperative complications and operative mortality are (1) nutritional support, (2) perfect anastomosis, and (3) postoperative respiratory and circulatory care. In cases of advanced esophageal cancer, radical operation—including extended lymph node dissection and combined resection of other organs—has been recommended.[15, 16] As a result, the operative mortality rate in patients with advanced carcinoma was higher (5.2%) than in patients treated because of early stage carcinoma (2.4%).

A characteristic histopathologic feature of early esophageal carcinoma, compared with other carcinomas of the gastrointestinal tract, seems to be an unexpectedly high incidence of vessel invasion and lymph node involvement, although these lesions are considered to be relatively early ones. Other investigators[17, 18] reported that the 5-year survival for early esophageal carcinoma without lymph node involvement was 80% to 90%. The prognosis, however, of patients with early cancer with lymph node involvement was as poor as that of those with advanced cancer. Among our 42 patients with early stage esophageal carcinomas, 17 (40.5%) had lymph node involvement or vessel invasion or both, and the 5-year survival was only 24.7%. Therefore our results suggest that the degree of malignancy of esophageal cancer cells is high, even at the early stage. If patients survive without a recurrence, they may be expected to enjoy a life of good quality.[19] Therefore we wish to stress that efforts must be made to detect esophageal carcinoma at the earliest possible stage. Lugol-combined endoscopy facilities detection of minute malignant lesions of the esophagus.

We thank M. Ohara for critical comments.

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Correspondence

Need for surgical wound dressing

Sir

I read with interest the paper by Chrintz *et al.* (*Br J Surg* 1989; **76**: 204–5). It is certainly not harmful to leave a sutured surgical wound uncovered; the wound can be more easily examined, costs in material and nursing hours are reduced and the patient can more easily move and carry out his personal hygiene.

Why apply a dressing to the wound during the first 24 hours? As long ago as 1951, following the example of my Master, Professor Georges Thomeret, I never have applied a dressing in the operating room on sutured surgical wounds, wherever they were located. All my fellows and students are taught to do so and in the course of time many surgical wounds have been left completely undressed. Of course, this method implies a perfectly sutured wound, free of any drop of blood that might soil either linen or bed sheets.

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Surgical glove perforation

Sir

In the February 1989 issue Dr A. J. Hamer referred to his fine device for discovering holes in surgical gloves (*Br J Surg* 1989; **76**: 206). What he states is undoubtedly correct and his device is probably worthwhile. It is re-invented every few years, but I believe that we originally described it in 1959. Our description has been referred to rather frequently. A somewhat similar device was also described in about 1960 in the Canadian literature as well as in the *Lancet* in 1958.

Unfortunately, in the July issue of the *American Journal of Surgery* in 1972, Joseph Miller showed that surgical rubber gloves become permeable to an electric current after a period of time which varies from 30 min upwards (this has recently been confirmed in the UK). Fletcher Miller and his associates also described this instrument as a new invention in 1966, but, unfortunately, Joseph Miller's problem has not yet been overcome and so I would warn users of such an instrument of false results which may cause them problems.

W. C. Beck

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Author's reply

Sir

I am grateful for Mr Beck's comments concerning my device. The principle of monitoring the drop in electrical resistance across a rubber glove due to a glove puncture is indeed not new, but the devices previously described all depended upon currents within the milliampere range for such detection[1–3]. The operator would also have to stop operating for a moment to dip his hands into a bowl of saline. British Standard BS5724 only allows currents of 100 μA or less to be applied directly to the patient's skin for monitoring purposes and, as my device only passes 9 μA or less, it is safe for continuous peroperative use, allowing the surgeon to operate uninterrupted.

The observations of Miller are interesting, although in my series on only one occasion (of the 41 when the alarm sounded) was there no apparent puncture, or wet gown sleeve touching the wound[4].

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Antibiotic prophylaxis and postoperative sepsis after cholecystectomy

Sir

The article by Wells *et al.* (*Br J Surg* 1989; **76**: 374–7), concerning the relationship between bile colonization, high-risk factors and postoperative sepsis, mirrored the results of a consecutive series of 504 cholecystectomies from the Westminster Surgical Unit[1] (*Table 1*).

Wells *et al.* conclude that, despite prophylactic antibiotics, bile colonization remains the major factor associated with postoperative sepsis. This is in agreement with our results. They did not compare their study group with a control group, justifiably, in view of the current body of evidence that demonstrates the value of antibiotics in biliary surgery.

In our own analysis the most common cause of wound infection was *Staphylococcus aureus*, not biliary organisms, for those patients receiving no prophylaxis. In those patients who received antibiotic prophylaxis, the incidence of *S. aureus* wound infections was significantly reduced.

Table 1 *Bile infection and wound infection in a consecutive series of 504 cholecystectomies*

	Positive bile culture	Positive bile culture with wound infection	Same organism in bile and wound infection	Negative bile culture with wound infection	Negative bile culture with *S. aureus* wound infection
Prophylactic antibiotics ($n=379$)	79/379 (21)	12/79 (15)	8/12 (66)	14/300 (5)	9/14 (64)
No antibiotics ($n=125$)	21/125 (17)	9/21 (43)	5/9 (56)	23/104 (22)	16/23 (69)
Significance (χ^2)	—	$P<0.01$	—	$P<0.001$	—

Values in parentheses are percentages

We would suggest that it is because of, not despite, antibiotics that bile colonization is the major factor associated with postoperative sepsis. This is more in line with the study by Willis *et al.*[2] who showed that in the absence of prophylactic antibiotics (*not* in the presence of prophylaxis, as quoted by Wells) wound infections were more commonly exogenous, a finding confirmed by Van Leeuwen[3].

It is because of this that we would agree with Wells in concluding that selective administration of antibiotics is inadvisable, and would add that, in choosing a suitable antibiotic, one should be chosen that has an antistaphylococcal activity.

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1. Menzies D, Ellis H. *Staphylococcus aureus*—a major cause of postcholecystectomy wound infection. Paper presented at the 2nd world congress on Hepato-pancreato-biliary surgery, Amsterdam, June 1988.
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Recessive mutation, chromosome deletion and cancer

Sir

The review by J. Berne and colleagues on recessive mutation and chromosome deletions leading to cancer (*Br J Surg* 1989; **76**: 327–30) introduces the important topic of specific DNA changes in cancer. Since the application of powerful molecular techniques to clinical material is a rapidly progressing field, recent advances in the study of breast and colon tumours merit a further note. As the authors mention, loss of heterozygosity for genes on the short arm of chromosome 11 in breast cancer and the long arm of chromosome 5 in colon cancer is well documented. However, more recent work indicates that chromosome 17 may be of prime importance in both cancers. Loss of DNA (allelic loss) from part of the short arm of chromosome 17 (17p) was identified in over 60 per cent of breast cancers studied[1,2]. Studies by the authors extending the initial series[1] suggest that allelic loss of 17p may occur in over 70 per cent of breast tumours. It has been proposed[2] that partial loss of 17p is associated with both genetically high risk forms (bilateral or familial) and sporadic breast cancer.

Eighty per cent of colon neoplasms have partial deletions of 17p (Reference 3), with particular loss of genetic material from that region of 17p containing the transformation-associated p53 gene[4]. It therefore appears that in breast and colon cancer there is a common region of deletion of the short arm of chromosome 17. This may result in loss of tumour suppressor function of the p53 gene and act as a crucial step[5] in the carcinogenic pathway.

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Radioisotope imaging in the evaluation of vascular grafts

Sir

We read with interest the article '^{111}In-labelled leucocyte imaging in vascular graft infection' by Berridge *et al*. (*Br J Surg* 1989; **76**: 41–4).

We have recently used radioisotope imaging in the evaluation of vascular graft infection, and would confirm the value of these techniques. Berridge *et al*. suggested that the use of technetium-99m might confer benefits compared with the other available radioisotopes, and we would support this suggestion by reference to a recent case.

A 68-year-old woman had undergone an aortobifemoral graft in another centre in 1982. In July 1988 she presented with an inflamed false aneurysm at her left groin anastomosis. This was successfully repaired. *Staphylococcus aureus* was grown from the small length of excised Dacron® (E.I. du Pont de Nemours and Company, Edinburgh, UK) graft. This was treated with flucloxacillin.

Subsequently, a small sinus developed in the left iliac fossa incision which failed to heal in spite of further antibiotics. In January 1989 she presented with a red hot swelling in the right groin. A sinogram on the left did not demonstrate connection with the graft.

To determine whether the graft was infected, a technetium-99m hexametazime (HMPAO)-labelled leucocyte (CERETEC, Amersham International plc, Amersham, UK) scan was performed. This identified increased uptake along the whole length of the limbs of the graft. The vertical part of the graft did not seem to show increased uptake (*Figure 1*). A gallium scan for comparison (*Figure 2*) only showed uptake in the right groin.

At subsequent removal of the graft, pus was found along the limbs of the graft but not involving the vertical portion of the graft.

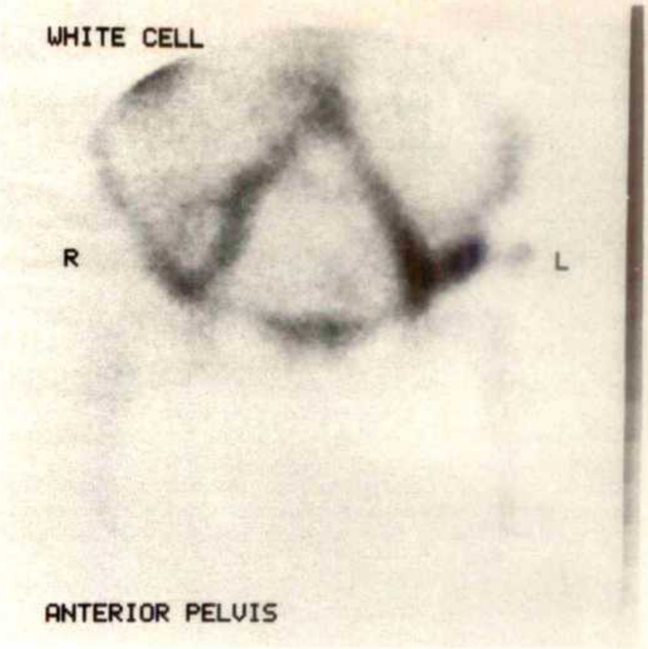

Figure 1 *Technetium-99 m scan of aortobifemoral graft*

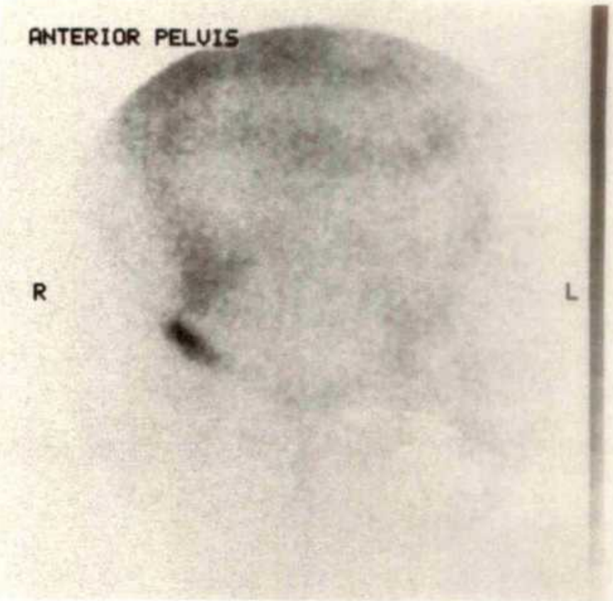

Figure 2 *Gallium scan of aortobifemoral graft*

Berridge *et al*. found no evidence of diffuse uptake in their aortic grafts and suggested that technetium-99m HMPAO might be particularly useful in this context, which this case would seem to illustrate.

Additional benefits of using technetium-99m HMPAO for these scans are its greater availability, a potential for making these scans less expensive, and, furthermore, allowing a diagnostic conclusion within 4 h, compared with the 48–72-h period required for other radioisotopic techniques. In view of these facts we would contend that technetium-99m HMPAO-labelled leucocyte scanning is the method of choice in the radioisotopic evaluation of vascular graft infection.

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Inguinal hernia repair

Sir

In the paper by Mr Marsden (*Br J Surg* 1988; **75**: 263–6) and in the subsequent correspondence by Mr Tinckler (*Br J Surg* 1988; **75**: 499) and Mr Kirk (*Br J Surg* 1988; **75**: 499), a variety of older techniques, including excision of the spermatic cord, are advocated for primary and recurrent inguinal hernia repair. Mr Barwell (*Br J Surg* 1988; **75**: 931) recommends that a controlled trial of an older technique *versus* the Shouldice repair should be conducted; however, the correspondent admits that he is too biased by the success of the Shouldice repair to take part. In the absence of this now mandatory yardstick of scientific judgement, a somewhat arbitrary preference may prevail for the most common surgical procedure undertaken on adult males in district hospitals[1].

In 1985, we started a prospective controlled trial comparing the Bassini and Shouldice repairs. Five hundred and fourteen primary and 86 recurrent hernias were enrolled up to April 1989, when entry was terminated. The Cox multiple regression procedure[2] was applied in a multifactorial analysis of prospectively defined recurrence risk factors. Highly significant differences in cumulative recurrence rates have become apparent in primary repairs (6·0 per cent for Bassini *versus* 0·9 per cent for Shouldice) and in recurrent repairs (11·1 per cent for Bassini *versus* 2·8 per cent for Shouldice). Recurrent hernia and hernial sac diameter $\geqslant 8$ cm were statistically significant risk factors in the Bassini but not in the Shouldice group.

Outstanding results of single institutions in hernia repair have not demonstrated whether these results were due to superiority of specialization or to superiority of method; it is noteworthy that Bassini reported a recurrence rate of only 2·8 per cent 100 years ago[3]. To our knowledge, this is the first trial showing the superiority of the Shouldice method in the routine practice of a busy general surgical unit.

Whilst in 1890 Bassini[3] published a letter of recommendation by a superior military officer in support of his achievement, we adhere to the controlled trial to demonstrate that the Shouldice repair is the first scientifically tested progress since the original Bassini repair.

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N. Fuchsjäger

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Vienna
Austria

1. Editorial. *Lancet* 1985; **i**: 1080–1.
2. Cox DR. Regression models and life tables. *J R Stat Soc* 1972; **343**: 187–220.
3. Bassini E. Über die Behandlung des Leistenbruchs. *Arch Klin Chir* 1890; **40**: 429–76.

Book reviews

Operative Hand Surgery. 2nd ed.

D. P. Green. 210 × 260 mm. Pp. 804 + 1648 + 2442. Illustrated. 1988. Edinburgh: Churchill Livingstone. £175 00.

The second edition of this comprehensive textbook on operative hand surgery is a welcome successor to the first. The overall plan to describe several procedures, the indications for them and the personal preference of the author is ideal for all those interested in hand surgery, from residents to the very experienced. Each chapter is extensively referenced and the illustrations throughout the book are first class.

The striking feature of the book, apart from its overall excellence, is its layout which, being alphabetical, produces an unusual distribution of topics. Thus in Volume Two there are four chapters on fractures and dislocations, but also other chapters in Volume One. Similarly, there is an excellent chapter on free skin flaps in Volume Two, but a whole section devoted to skin cover in Volume Three. The section on incisions in the hand and wrist is in the midportion of the third volume. This layout is confusing to the reader but should not be allowed to detract from the overall quality. The new edition also contains eight new chapters on microsurgery, which seems excessive when compared with the space allocated to some other subjects, for example, 20 pages for infections of the hand.

It is difficult to particularize about the chapters in the book, most of which are comprehensive, authoritative and well illustrated. We found the chapters on skin preparation and use of tourniquets, amputations, carpal dislocations and instability, nerve repair and grafting, open injuries of the hand and skin flaps particularly valuable.

It would have been valuable to have seen a more critical assessment of the indications and the results for some of the procedures described, for example, vascularized joint transfers.

Overall this is the best presented, best written and best researched book on hand surgery presently available in the English language. We recommend it most strongly for all those who have an interest in hand surgery.

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Hardy's Textbook of Surgery. 2nd ed.

J. D. Hardy. 203 × 280 mm. Pp. 1348. Illustrated. 1988. Philadelphia: J. B. Lippincott Company. £25 00.

This is a large, dense, compact textbook of surgery covering all aspects from basic and support considerations to general surgery in all its aspects, cardiothoracic surgery, paediatric surgery, plastic and reconstructive surgery, orthopaedic surgery, urology and neurosurgery. In addition, there is a short chapter on gynaecological surgery as it affects the general surgeon and there is a chapter dealing specifically with the hand. There are also good chapters on immunobiology and transplantation and at the end there is a practical chapter presumably aimed at the practising resident. The book is lavishly illustrated, both with line drawings and black-and-white photographs, and contains such interesting titbits as pictures of spiders of North America most likely to produce a dangerous bite.

It is lavishly referenced both in terms of up-to-date papers and a general bibliography; the index appears to be comprehensive and it is set out in double columns to the page. I am impressed with the clarity of the printing given the quality of paper used. It is certainly not a book for the British undergraduate medical student, neither is it one which I suspect a fellowship candidate would want to buy. On the other hand, it is so comprehensive that it would make an extremely good reference book when required. For example, when other texts had failed me I was able to find some information here about tumours of Zuckerkandl's organ. It would therefore be a valuable asset to any surgical library for this purpose!

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Management of Abdominal Hernias

H. B. Devlin. 216 × 280 mm. Pp. 203. Illustrated. 1988 London· Butterworths. £60.00.

This book is a practical treatise on abdominal hernias of a manageable length that should satisfy both the learner and the experienced surgeon There is a tendency to think that the larger multi-author book is the ultimate achievement and that for hernias this has already been achieved by the Nyhus and Harkins book 'Hernia' Such a book may act as an encyclopaedia but it is never read from start to finish. The other type of book is by a single author, it is shorter and may be less comprehensive but its message is more easily transferred because of its singular experience and uniformity. This book on abdominal hernias delivers its one-author message in an exemplary way and is far more likely to be read from cover to cover. The fact that some parts have been previously published must be interpreted as indicating that their contents have withstood the test of time well. There is no need to excuse this new book as the author does in his Preface. The past is important and Bassini is just as important as Shouldice. Similarly, anatomy is emphasized as it should be but on equal terms with the economics of hernia repair The line drawings of Gillian Lee are to be specially recommended because they are clear, accurate and appreciated as true representations by the surgeon. The format of double columns allows for well-spaced illustrations and subheadings, and the relatively heavy paper and clear type makes this a pleasant book to hold and read Its presentation is a credit to Butterworths. As most of us start learning surgical techniques with hernia repair and proceed to earn our living repairing hernias, and since hernia repair is one of the commonest operations and a frequent cause of lost time at work, this book deserves a wide circulation to all surgeons at any stage of their career. This review copy will be left accessible to the junior staff; it belongs neither to the coffee table nor to the library shelf; it should become worn and battered with use

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Progress in Vascular Surgery

J. S. Najarian, J. P. Delaney. 235 × 155 mm. Pp. 469. Illustrated 1988. Chicago. Year Book Medical Publishers Incorporated. £52.50

This book is based on lectures from a course in surgery at the University of Minnesota Medical School. Lectures often transpose poorly to the written page unless carefully edited. The book is not a review of recent progress in vascular surgery as the title suggests and more is the pity Several chapters titillate the reader with headings such as 'What's new in . . .', 'Recent improvements in . . .' but turn out to contain standard material long associated with their authors. In the chapter on popliteal and tibial bypass, for instance, no mention is made of the Miller cuff, the Taylor patch, arteriovenous fistula or the use of deep leg veins, all recent techniques currently undergoing evaluation Similarly, the skew flap technique is omitted from the chapter on amputation The views on carotid surgery indications might give some neurologists an apoplexy. Nevertheless, amongst all this material are some nicely written pieces on such difficult subjects as Raynaud's phenomenon. Panel discussions at the end of each section are published verbatim. This is tedious for the reader because to gain useful information one has to sift through phrases such as 'let us have a hand of applause for the panel' (surgeons always have been self-congratulatory) and even 'Nancy, give him some heat'. To include a discussion among panellists on the suicide of a colleague seems in poor taste at the very least The English in the panel discussions is even worse than that in the written chapters. Sentences stretching over seven lines and containing such words as 'knowledgeably' require the blue pencil. The editors seem to have done little more than arrange the chapters in order

While containing much useful information this book cannot be recommended; the cost is high at £52.50 but one can fairly say that the language, if not the book, is priceless.

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Notices and announcements

19–21 July 1989
British Association of Paediatric Surgeons: XXXVI Annual International Congress
Nottingham, UK
Information. Dorothy Grant, Congress Secretary, British Association of Paediatric Surgeons, The Royal College of Surgeons of Edinburgh, 18 Nicolson Street, Edinburgh EH8 9DW, UK

21–24 August 1989
4th International Symposium on Obesity Surgery
London, UK
Information: Mr E. R. T. C. Owen, Academic Surgical Unit, The Queen Elizabeth Queen Mother Wing, St. Mary's Hospital, Praed Street, London W2 1NY, UK

27 August–1 September 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Informtion: International Congress and Convention Association, PO Box 50006, Tel Aviv 61500, Israel

7–9 September 1989
Surgical Efficiency and Management Club
Maastricht, Holland
Information. Professor Stig Bengmark, Lunds Universitet, Institutionen for Kirurgi, 221 85 Lund, Holland

8–9 September 1989
4th South-East-European Symposium of Paediatric Surgery
Graz, Austria
Information Professor Dr H. Sauer, Department of Paediatric Surgery of the University of Graz, Heinrichstrasse 31, A 8010 Graz, Austria

9–10 September 1989
Magnetic Resonance Imaging for Technologists Seminar: A Practical Introduction
Philadelphia, USA
Information. Janice Ford or Nancy Fedullo, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104, USA

10–15 September 1989
3rd International Symposium on inflammatory Bowel Diseases
Jerusalem, Israel
Information: International Congress and Convention Association, P.O Box 5006, Tel Aviv 61500, Israel

11–16 September 1989
33rd World Congress of Surgery
Toronto, Canada
Information: 33rd World Congress of Surgery, Congress Canada, Congress Management, 73 Richmond Street West, Suite 300, Toronto, Canada M5H 1Z4

17–26 September 1989
Frontiers in Gastroenterology: Colorectal Disease
Birmingham, UK
Information. Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

19–20 September 1989
New Trends in Pelvic Pouch Procedures
Bologna, Italy
Information. R. M. Società di Congressi srl, Via Ciro Menotti 11–20129, Milano, Italy

20–23 September 1989
21st European Pancreatic Club
Glasgow, UK
Information: Mr C. W. Imrie, Consultant Surgeon, Royal Infirmary, Glasgow G4 0SF, UK

21–23 September 1989
Annual General Meeting of the Association of Surgeons in Training
Cardiff, Wales, UK
Information: Mr B. Taylor, Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

22–24 September 1989
Association of Colon and Rectal Surgeons of India
Soura Sringar, India
Information: Dr N. A. Wani, Organizing Secretary, Room No. 1318, Sher-i-Kashmir Institute of Medical Sciences, Soura Srinagar, India

27 September–1 October 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Information: The Secretariat, 2nd International Conference on Gastrointestinal Cancer, P.O. Box 50006, Tel Aviv 61500, Israel

29 September 1989
Progress in Microsurgical Training, Research and Clinical Support. The Sixth Annual Meeting of the Society of Microsurgical Specialists
Buffalo, New York, USA
Information: Elaine Lavigne, University of Vermont, Microsurgical Laboratory, Give Building E-302, Burlington, Vermont 05405, Massachusetts, USA

4–7 October 1989
Principles of Colon and Rectal Surgery
Minneapolis, USA
Information. Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast , Minneapolis, Minnesota 55455, USA

5–7 October 1989
2nd International Tissue Expansion Symposium
Marseille, France
Information: Sud Congres Services, 4 bis, Impasse du Roc-Fleuri, 1300 Marseille, France

15–21 October 1989
Recent Advances in Pancreaticobiliary Surgery.
Edinburgh, UK
Information: Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

16–20 October 1989
Sixth World Congress on Medical Informatics MEDINFO 89
Beijing, China
Information Dr Phil R Manning, Chairman, Scientific Programme Committee, MEDINFO 89, USC School of Medicine, 1975 Zonal Avenue, KAM 317, Los Angeles, California 90033, USA

2–3 November 1989
International Soft Tissue Sarcoma Conference
London, UK
Information: Miss J Mountsteven, Conference Centre, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information: J. P. Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

23–24 November 1989
Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland
Dundee, UK
Information: Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

3–9 December 1989
Breast Cancer: New Developments in Biology, Diagnosis and Treatment
UK
Information. Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr Joseph W. C. Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

20–21 January 1989
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

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Essential Surgical Practice Second Edition

Edited by
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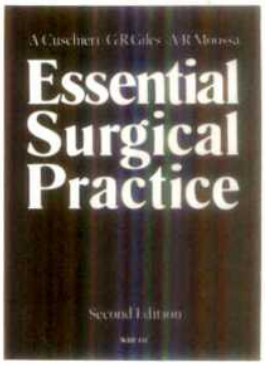

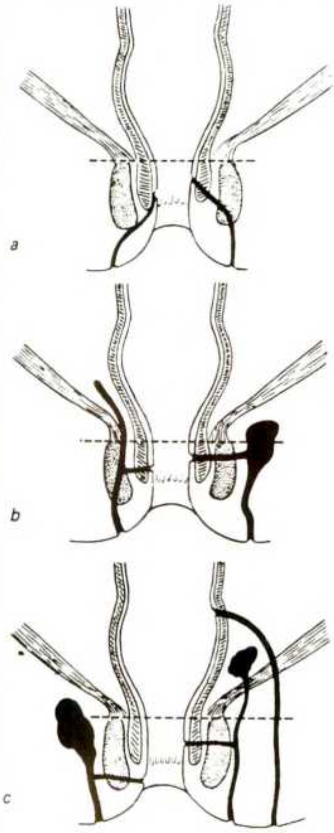

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The New England Journal of Medicine

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'It should be a great success on both sides of the Atlantic.' *Annals of the Royal College of Surgeons*

'. . . Covers very well an extensive range of material which is well illustrated and readily comprehensive. It should be very useful equipment for the trainee surgeon for the Australasian college.'
New Zealand Medical Journal

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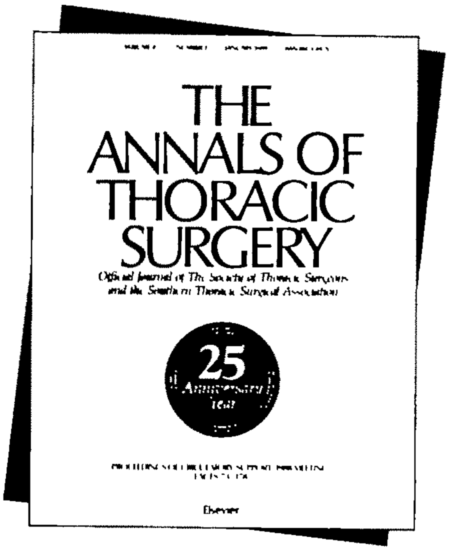

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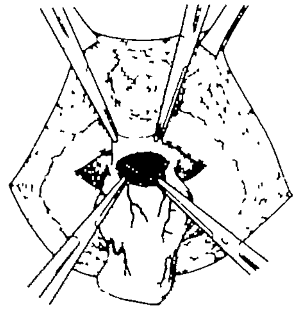

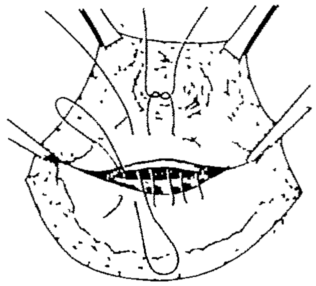

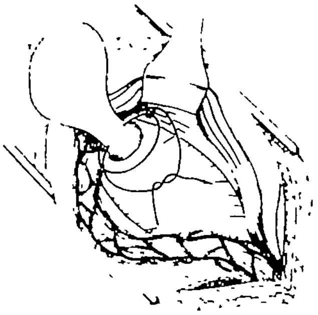

Leading article

Br. J. Surg. 1989, Vol. 76, August, 771–773

Palliative treatment of hepatic tumours

Approximately 25 per cent of all patients with cancer have or will develop hepatic metastases and less than 20 per cent of these individuals can be considered for radical liver surgery. For the remainder other effective treatments are desirable, given the poor quality of life for most patients with liver metastases. Earlier studies of the natural history of liver metastases, carried out some 20 years ago by my group and others, showed that the median survival time in primary liver cancer was only 2 months and that in the case of metastases from pancreatic, gastric, breast and colorectal cancer it ranged from 2 to 5 months. As only the most healthy patients receive active treatment, with its risk of severe side-effects, we have suggested as a guideline that any treatment which does not quadruple the survival figures mentioned above should not be used outside the context of controlled studies. Employing this definition, most of the treatments now used should still be regarded as experimental, particularly in the case of metastases from colorectal cancer.

Chemotherapy for liver metastases

During the past 30 years, chemotherapy has been the leading method of treatment for liver metastases Despite varied administration schedules and routes (intra-arterial, intraportal, intraperitoneal), use of sophisticated apparatus such as implantable pumps, and varied mixtures of cytostatic agents, we seem to have added little to the success of this approach. It has also proved difficult to control tumour growth without affecting normal tissues and producing severe side-effects. Another important problem so far neglected is that after each treatment cycle there is rapid compensatory growth which often makes the end result the same as if no treatment had been given. It has also been observed that treatment directed towards one region may well result in compensatory growth outside the region. For example, regional therapy for hepatic tumours often appears to be associated with accelerated growth of extrahepatic tumour.

Most of the experience to date favours treatment repeated at short intervals and, if possible, throughout life. In our view, the goal should be to retard and control tumour growth by continuous therapy. Problems with systemic infusion chemotherapy, notably severe side-effects and difficulties with long-term maintenance of treatment, have stimulated study of alternative routes of administration. In a recent randomized study, regional intra-arterial chemotherapy was compared with systemic venous chemotherapy[1]. Objective signs of response were seen in 62 per cent of the first group and 17 per cent of the second group. However, there was no significant difference in actuarial survival rates at 24 months (22 and 15 per cent respectively). In addition, continuous intra-arterial 5-fluorodeoxyuridine chemotherapy was followed by significant problems including chemical hepatitis (79 per cent), biliary sclerosis (21 per cent), peptic ulcers (17 per cent) and gastritis/duodenitis (21 per cent).

Many attempts have been made to reduce the systemic toxicity of cytostatic drugs For example, Onahara *et al.*[2] used sodium thiosulphate intravenously in parallel with aggressive intra-arterial infusion of cisplatinum. They reported almost no side-effects despite the fact that the efficiency of treatment was not reduced.

Ischaemic and metabolic treatment

The Nobel prize winner, Warburg, suggested 50 years ago that metabolic manipulation could be effective in the treatment of tumours. Such manipulation could include reduction of oxygen supply and the use of glucose analogues to perturb glucose metabolism. For more than 25 years, our own group has studied ischaemia as a treatment for hepatic tumours. Initially, we considered that the liver was an ideal organ for this treatment as hepatic metastases are supplied solely by the hepatic artery, while the normal parenchyma has a dual supply from the hepatic artery and portal vein. Attempts to retard tumour growth by hepatic artery ligation, total hepatic dearterialization and intermittent hepatic artery occlusion over some months were largely unsuccessful. No improvement in survival was apparent when results were compared with the natural history, although there were encouraging exceptions. For example, extremely good results have been obtained in some patients with carcinoid

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tumours (tumour regression, disappearance of symptoms, reduction of 5-hydroxyindole acetic acid excretion) for periods of up to 60 months. Carcinoid tumours are very vascular and may be particularly sensitive to ischaemic treatment. In addition, the compensatory growth is much slower than that observed in most other tumours[3].

It is now quite clear that tumours are very sensitive to ischaemia. Vascular occlusion for less than 1 h may induce irreversible changes, and it has become obvious that the endothelial cells within tumour vessels are most sensitive to mechanical, toxic and metabolic injury. This is in contrast to the tumour cells, which are generally rather resistant. It is well known that tumour vessels have no smooth muscle layer and have instead an extremely well developed intima. Denekamp[4] has suggested that the endothelial cells have a much higher (up to 2000 times greater) metabolic and replication rate than any other tissue in the body. It is likely that even very brief ischaemia leads to irreversible changes in the endothelium with swelling, blockage of flow and secondary effects on the tumour cells. It could well be that other methods of treatment such as cytostatic treatment and irradiation involve the same mechanisms.

It was long believed that growth of tumour cells was autonomous and that these cells were incapable of regenerative and compensatory growth. However, studies in our laboratory have shown that a replication peak occurs 24 h after a 1-h period of ischaemia. This offers interesting potential for a combination of intermittent ischaemia followed by antimetabolite treatment 20–24 h later. We have collaborated in developing an implantable device which allows repeated occlusion of the hepatic artery. We have used the device to occlude the hepatic artery twice daily for life, ischaemia being effected on an ambulatory basis by the patients themselves. Our early results offer promise[5].

We are no longer convinced that ischaemia is applicable only to tumours in organs with dual vascular supply, and have used the approach in patients with portal venous obstruction and in those with cancers of other organs. Hepatocellular carcinoma is usually resistant to almost any treatment, including total hepatic dearterialization. To our surprise, pronounced tumour shrinkage has been observed recently in two patients treated with pulsed ischaemia, both of whom had portal venous occlusion which made the repeated ischaemia total.

Embolization

Alternative techniques for ischaemic treatment involve embolization of microspheres of starch or albumin to obstruct arterial tumour flow. Redistribution of blood flow to hepatic tumours has also been attempted with drugs such as noradrenaline and/or propranolol[6]. The main problem with such methods is that they require an intra-arterial catheter, which usually prevents daily self-administered ambulatory treatment and also makes it difficult to achieve intermittent occlusion. Such drawbacks also apply to lipoidal embolization.

Despite the flood of publications on embolization, most of the results are based on anecdotal reports or uncontrolled studies. However, success has been reported in patients with such diseases as hepatocellular carcinoma and metastases from melanoma, islet cell tumours and colorectal cancer. Despite the fact that an objective response is often seen, significant prolongation of median survival has not been demonstrated.

It is also important to underline the morbidity associated with embolization. Nausea, vomiting, fever, abdominal pain, paralytic ileus and transient elevation of liver function tests are seen in almost every patient, but rarely occur after pulsed ischaemia. In addition, severe complications such as gallbladder infarction (11 per cent), acute pancreatitis (4 per cent), delayed formation of gallstones (2 per cent), hyperuricaemia (1 per cent), gastroduodenal bleeding (1 per cent) and hepatoma rupture (1 per cent) are reported [7]. Serial assessment after gel-foam embolization has shown severe liver damage, particularly in patients with underlying hepatic disease[8]. An interesting study comparing the results of repeated arterial embolization, single embolization plus monthly 5-fluorouracil, and monthly 5-fluorouracil alone in patients with unresectable hepatocellular cancer has recently been published[9]. Repeated embolization proved the most effective treatment: complete response was seen in one patient in this group and a partial response occurred in 62 per cent of patients (compared with 48 and 10 per cent in the two other groups). One can speculate that if it was possible to repeat embolization at shorter intervals treatment might be more effective.

Future treatment

It is my strong belief that attempts should be made to develop a palliative treatment for patients with liver tumours which is simple, can be performed on an ambulatory basis for life, involves active participation by the patient, and which has minimal or no side-effects. Such treatment should not reduce mental and physical activity. At present the goal should be growth control and not cure.

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Aids in the diagnosis of acute appendicitis

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Methods used to improve the accuracy of diagnosis of acute appendicitis are reviewed. Laparoscopy, barium enema, ultrasonography and computer assistance have all been shown to improve accuracy, but no one method is of proven superiority. Such diagnostic aids or intensive in-hospital observation must be used to reduce the 15–30 per cent negative laparotomy rate when acute appendicitis is suspected, without increasing the incidence of appendiceal perforation.

Keywords: Acute appendicitis, laparotomy, diagnosis

Although abdominal surgeons have been confronting acute appendicitis for more than 100 years, its diagnosis remains elusive. Some senior surgeons can diagnose acute appendicitis accurately in over 80 per cent of cases[1,2] However, in most cases, it is more junior surgeons who are responsible for deciding whether a patient with right iliac fossa pain should be operated on or not. Their decision may be wrong about 50 per cent of the time[1–5]. Accuracy rates, illustrated by the number of normal appendices removed, will also vary according to the patient population involved Among young male patients the negative appendicectomy rate is relatively low (5–22 per cent[1,6–12]), while for women of childbearing age the figure may be as high as 30–50 per cent[1,6,7,9–11,13–17]. In young children the diagnosis may be wrong in 30–46 per cent of cases[7,10,11]. The difficulty of diagnosing acute appendicitis in old age is reflected by the high incidence of perforation, 60–90 per cent in many reports[7,10,13,14,18–21], rather than by a high rate of negative appendicectomy[9,14,21,22]. Diagnosis is also difficult during pregnancy and may result in both maternal and fetal mortality[13,23–25]. In the latter groups of patients the diagnosis is difficult for doyen and novice alike. Appendicitis is a great leveller in surgery, an antidote to diagnostic complacency.

The problem arises because patients presenting with acute right iliac fossa pain may have acute appendicitis, which requires surgery, or some other cause of pain, which may not The surgeon resolves the dilemma in one of two ways: by observation until the signs and symptoms make the diagnosis more obvious or by immediate operation. As the incidence of perforation is usually proportional to the duration of the disease process, traditional teaching has encouraged surgeons to operate even when the diagnosis is probable rather than wait until it is certain. This teaching has been challenged by some[8,26–30] who have shown that intensive observation in hospital can decrease the incidence of negative appendicectomy without increasing the rate of perforation. Prolonged observation is, however, not an ideal solution as it is expensive to the health services. Furthermore, no-one can be sure how many of these patients in fact have appendicitis which resolves spontaneously under observation only to recur at a later date[29,31–33].

The morbidity and mortality rates associated with appendicitis are greatly increased when perforation ensues[7,10,11,13,14,31]: wound infection rates may treble, intra-abdominal abscess formation increases 15-fold[13] and mortality may be 50 times greater[34]. Appendiceal perforation can also cause tubal infertility[35]. It is therefore obvious that the aim of the surgeon must be to prevent perforation at any price. The price is the high rate of removal of a histologically normal appendix, which is not inexpensive as it carries with it a complication rate not much lower than that after removal of a pathological appendix[6,7,9–11,13,14,36–38]. The operation of negative appendicectomy is accompanied by the usual spectrum of immediate postoperative complications in up to 15 per cent of patients[13]. Some patients may even die after negative appendicectomy[6,10]. Additional patients may suffer late complications such as intestinal obstruction[10,16,37], incisional hernias[37] and sterility due to fimbrial adhesions[6,15,39,40]. The latter postulate has, however, been recently refuted[35]

Thus, a surgeon confronting a patient suspected of having acute appendicitis is wedged between the Scylla of perforation and the Charybdis of negative appendicectomy. He or she has, however, been taught the axiom that the number of negative appendicectomies will be inversely proportional to the number of perforations. It appears, therefore, that surgeons have created for themselves a surgical security zone which allows them to accept a 15–30 per cent negative laparotomy rate with impunity[6,14,41–43].

The aim of this review is to show that measures are available to aid in the diagnosis of acute appendicitis rendering this orthodox surgical teaching obsolete.

White blood cell counts

This diagnostic test will be reviewed not because it has great value in the diagnosis of acute appendicitis but because it is so universally used and therefore needs to be placed in perspective.

It is clear[44–47] that 80–85 per cent of patients with acute appendicitis will have a total white blood cell count of over $10\,000/\mathrm{m}^3$ Neutrophilia of >75 per cent will occur in 78 per cent of patients[44,48]. When the white cell count and neutrophil count are taken together <4 per cent of patients with acute appendicitis will have normal levels[44,46] However, the white cell count is raised in 25–70 per cent of patients with other causes of acute right iliac fossa pain[46–48]. Leucocytosis increases with the duration of the disease process[44], but even a perforated appendix may present with a normal white cell count Of note is the observation of some[47] who found that, if the white cell count is repeated after some hours, it remains high in patients with acute appendicitis but tends to fall in those without appendicitis. Others have reported that the white cell count[46] and neutrophil count[49] are especially sensitive in children. In elderly patients with appendicitis the white cell count has been variously reported as being either reliable[14,18,21,22,44,50] or unreliable[19,34,51].

Thus, although a raised white cell count is a highly sensitive test for acute appendicitis, it is rendered almost useless by its low specificity and it has little diagnostic value[6,9,13,14,36,41,47,48]. Where the white cell count is at variance with the clinical signs, the latter should take precedence[48]. The only value of the white cell count would seem to be to prompt observation rather than operation in a patient who has equivocal features of appendicitis together with a normal count[44–46].

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Plain radiography of the abdomen

Although there is no radiological sign that is pathognomonic for the diagnosis of acute appendicitis, plain radiography of the abdomen has been used for this purpose since 1906[52] It is a highly inaccurate investigation and is mentioned here only to discourage its use.

The use of plain abdominal radiography is based on the demonstration of one or more of the following signs[52–61]: faecolith of the appendix, gas in the appendix, air–fluid levels or dilatation of the terminal ileum, caecum or ascending colon (i.e. signs of localized paralytic ileus), deformity, oedema or obliteration of the caecal shadow, blurring or spasm of the right psoas muscle, scoliosis of the lumbar spine, widening or obliteration of the properitoneal fat line in the right iliac fossa, haziness or disappearance of the pelvic peritoneal fat stripe, density or haziness over the right sacroiliac joint, and free intraperitoneal or retroperitoneal gas. Not one of these signs is specific for acute appendicitis and they may be found in patients with other causes of right iliac fossa pain and in many normal subjects

Any one or more of these signs have been found in 24–95 per cent of patients with appendicitis[52–60]. The sensitivity of the test increases with the degree of inflammation[52,53,56,59] and the expertise of the interpreter[57]. One study[61] found that 60 per cent of patients with positive radiographs did not have appendicitis. Another[55] found at least one of the signs in 38 per cent of 'normal' subjects. Other more recent studies have also found plain radiographs to be unreliable[9,14,22,36,62]. The incidence of positive radiographs among patients with causes of right iliac fossa pain not requiring surgery has varied between 4 and 73 per cent[52,53,59–61] It must be mentioned, however, that 1–10 per cent of the patients with false positive radiographs for appendicitis had other intra-abdominal diseases which required surgery, such as perforated ulcers or colonic diverticula, torsion of ovarian cysts and intestinal obstruction[52,53,60,61].

Furthermore, irradiation hazards, especially to two groups most frequently requiring elucidation, namely women of reproductive age and children, as well as the cost and overloading of radiology departments[58,61], make this investigation of low diagnostic yield especially unattractive.

Barium enema

A normal appendix can be filled with barium on barium enema examination while an appendix obstructed by the process of appendicitis will not allow the passage of barium. This is the premise on which the barium enema diagnosis of acute appendicitis is based However, both statements are open to question. The appendix of about 10 per cent of normal persons cannot be demonstrated on barium enema[60,63–66]. On the other hand, barium may entirely fill an inflamed appendix[59] or it may fill an appendiceal lumen without allowing the examiner to determine with certainty whether this represents the entire length of the lumen or not[67,68]. The appendix may be inflamed distal to the point reached by the barium. This latter situation of partial filling can usually, but not always, be diagnosed radiologically as the lumen will be cut off rather than tapering to a normal tip, which is described as bulbous. This cut-off is considered a highly reliable sign of appendicitis[60,64,65,69,70].

Therefore non-filling of the appendix alone is not pathognomonic of acute appendicitis and must be accompanied by signs of inflammation usually registered as deformity, spasm, displacement and/or thickening of the caecum, ascending or sigmoid colon or terminal ileum[59,60,64–66,69,71]. The examination is described as requiring no preparation and minimal pressure and manipulation of the abdomen, and is entirely free of complications including appendiceal perforation[59,60,63–66,69,71,72].

Two papers report a sensitivity and specificity of 100 per cent[69,71]. In four other studies[60,63 65] the sensitivity of barium enema ranges from 90 to 100 per cent and the specificity from 75 to 98 per cent. These results must be tempered by the fact that the examination was technically unsatisfactory or non-diagnostic in up to 16 per cent of cases, and these cases were excluded from the statistics[64,69,71]. Thus barium enema is highly accurate in the diagnosis of appendicitis although false positive examinations do occur, especially due to gynaecological diseases[60,64,73], and some discourage its use[14 22,67,68].

The great advantage of barium enema examination is that it is available in most hospitals and does not require special equipment other than that already available in most radiology departments. A further advantage is that barium enema can diagnose other diseases, which may be confused with acute appendicitis, such as colonic carcinoma, terminal ileitis and ischaemic colitis[63,70,72] Its disadvantages lie in its relatively high incidence of technical failure and its radiation hazard[14,58].

Ultrasound[34,74–85]

If the appendix can be seen on ultrasound examination this is taken to indicate the presence of acute appendicitis. If the organ cannot be seen, appendicitis is excluded. The appendix is seen as a blind-ending, immobile, non-compressible structure which cannot be displaced on pressure with the ultrasound probe. The varying echodensity of the lumen, mucosa and thickened wall of the inflamed appendix gives a characteristic ultrasound picture which has been dubbed a 'bull's eye' or 'target'. A faecolith in the lumen or fluid surrounding the organ are considered confirmatory signs of appendicitis. The examination will be non-diagnostic in 3–11 per cent of cases because of pain, guarding, obesity or overlying gas[77,80,82–84]. Among seven studies in the literature, the sensitivity ranges from 75 to 89 per cent and the specificity from 86 to 100 per cent[77,78,80–84] Less accurate results are reported in another study, but the authors claim that their equipment was not optimal[79] Poorer results are also reported for retrocaecal appendices[79], early appendicitis[85] and perforated appendices[80]. In other studies, however, the diagnosis of perforated appendicitis was found to be very accurate[82,85] Another factor detracting from some of the studies is the fact that some of the patients diagnosed ultrasonically as having appendicitis were not operated on[80,83,84]. The authors believe that these were mild cases which resolved spontaneously. One might argue that these patients should be regarded as false positives.

Besides being highly specific in diagnosing appendicitis in the hands of experts, ultrasound has further advantages. It is accurate in excluding diseases that do not require surgery (such as mesenteric adenitis, terminal ileitis, ureteric stones and especially gynaecological disorders) as well as diagnosing diseases other than appendicitis which do need operation (such as ectopic pregnancy[79,80,84]). Ultrasound is non-invasive and can be used in pregnancy[82]. Its main disadvantage lies in the fact that it requires special equipment and special expertise The latter may not be available 24 h per day[34,84]. Further disadvantages are its relatively low sensitivity in some studies and the fact that it is difficult to use in obese or distended patients[82–84].

Laparoscopy

Laparoscopy has the attraction of being the only investigation that can view the appendix directly The criteria used for the diagnosis of acute appendicitis are the identification of an inflamed appendix or the presence of signs of inflammation in the right iliac fossa when no other pathology can be found to account for this. Appendicitis is excluded if a normal appendix is seen or if another cause of intra-abdominal pathology is revealed to explain the clinical picture[15,16,39,40,86–89].

Previous laparotomies, obesity and abdominal distension are generally considered contraindications to laparoscopy[90–92]. In addition to patients in whom laparoscopy is contraindicated, a further 14 per cent of patients cannot be examined because of technical difficulties[40,93] Furthermore, the appendix cannot be directly visualized in 7–83 per cent of patients (usually about 15 per cent), but indirect signs may nevertheless point toward appendicitis[15,16,39,40,87,89,93].

Two papers report an accuracy of 100 per cent[86,88]. In six other studies the sensitivity varies from 70 to 100 per cent and the specificity from 73 to 95 per cent[15,16,39,40,87,93]. Jersky *et al* [39], however, point out various pitfalls: an appendix thought macroscopically to be inflamed at laparoscopy may nevertheless be normal. The appendix and Fallopian tube may be inflamed simultaneously. The appendix is often not seen throughout its length. Even if another convincing explanation for the clinical signs is revealed the patient may yet have appendicitis. Nevertheless, negative laparotomy can be obviated in as many as one quarter to one half of the patients by using laparoscopy[15,40,86,88–90,93]. In one study, the negative laparotomy rate was reduced to 1 per cent[87]. This occurs mainly because laparoscopy can accurately diagnose gynaecological conditions An additional advantage of laparoscopy is that it can diagnose other causes of an acute abdomen requiring surgery, such as perforated peptic ulcer. It can be used during pregnancy[15]

The major disadvantage of laparoscopy is its invasiveness. It requires a general anaesthetic (although some[88] perform laparoscopy under local anaesthetic) and is in fact an 'operation' that may result in many of the complications of any abdominal procedure. These complications are infrequent and usually minor, in the form of wound problems, but deaths[86] and life-threatening complications such as perforation of major blood vessels[93] have been reported. The incidence of these complications is, however, lower than after negative appendicectomy. Another disadvantage is that laparoscopy requires special equipment and expertise.

Computers

Structured data gleaned from history-taking and physical examination may be fed into a previously programmed computer, which can then make a diagnosis of acute appendicitis or non-specific abdominal pain. Such systems[94] have been used since 1972 in tens of thousands of patients in many centres, although predominantly in the UK It has been shown, using a computer, that the accuracy of distinguishing between acute appendicitis and causes of abdominal pain not requiring surgery increases to between 72 and 92 per cent compared with an accuracy of unaided clinical diagnosis of between 52 and 80 per cent[2–4,17,95–97]. Negative laparotomy rates drop from 18–37 to 6–10 per cent[2–4,17,95,96]. The incidence of appendiceal perforation drops from 22–36 to 4–12 per cent[2,4,95]. The mortality associated with appendicitis drops by up to 50 per cent[4,95]. Enormous financial savings accrue owing to lowered rates of complications and negative laparotomies, the number of bed-days required for observation of the patients and the decreased use of other ancillary investigations[3,4 95,96] These savings outweigh the cost of installing and running the computer[95]. A single study, however, has found that computer diagnosis was no more accurate than unaided clinical diagnosis[37]

Enthusiasm for computers has been tempered by various misgivings Some claim that it is difficult for untrained personnel to use a computer. It has been shown, however, that it is easy to use the system although it takes 2–3 months to glean the full benefit[98] Others are of the opinion that the computer is needed, but that the improvement in clinical diagnosis results not because of the computer, but because of improved clinical data gathering by the clinician[99] This is true to a certain extent, but it has been shown that clinical performance will again decrease if the surgeon is denied feedback from the computer[98] It has also been suggested that the database from one centre cannot be successfully transferred to another geographical area[98] This has been confirmed by some[37,100] but disproved by others[17,101]. In addition, clinicians may be reluctant to use computers in that they dehumanize or impinge upon the art of clinical diagnosis; but computers in fact stimulate the clinician to function more accurately and to gather clinical data more efficiently[2,4,17,95,96,101]. Finally, a point not emphasized in most of the reports is that in order to gather data for the computer one requires a conscious, communicative and co-operative patient[102] It is not possible to determine from most of the studies how many patients could not be 'computerized' because they were too young, too senile or otherwise unable to give a good history or respond adequately to clinical examination. Such patients constitute a group in which the diagnosis of the acute abdomen is most difficult[103,104]. This, however, does not occur frequently in the two studies that address the problem[2,94].

The attraction of computer diagnosis lies in the fact that it is eminently non-invasive and highly accurate. Its disadvantage is that it requires special equipment and training.

Miscellaneous

Included here are various other methods that have been used to diagnose acute appendicitis. As they have not been widely tested, their places in the armamentarium cannot yet be established.

Scoring systems

The patient's signs, symptoms and white cell count are given various scores. A patient who scores above a certain figure is considered to have appendicitis. The number of signs and symptoms included in the scoring system varies from 7 to 19 in four studies[38,62,100,102] One prospective study reports a sensitivity of 90 per cent and a specificity of 91 per cent for their system[100]. Negative appendicectomy rates could be reduced by about 30 per cent in three studies[38,62,100].

Computed tomographic (CT) scanning

CT scanning can diagnose acute appendicitis[105–108]. It is accurate for advanced cases but inaccurate in early appendicitis[105] Such a highly sophisticated and expensive apparatus can hardly be expected to be used in the day-to-day diagnosis of appendicitis, but may be of use in an occasional patient where diagnosis is very difficult[105,106]

Radioactive isotope imaging

A patient's leucocytes may be incubated with a radioactive isotope. After reinjection these leucocytes can be detected in an inflamed appendix on scanning. Technetium-99m[12,109] and indium-111[110] have been used. These three studies revealed a sensitivity of 83–89 per cent and a specificity of 92–100 per cent. In one study[109], however, the method was shown to be unreliable in diagnosing appendicitis in women, so it may need to be supplemented with an ultrasound scan to exclude gynaecological disease[12].

Diagnostic peritoneal aspiration or lavage[104,111–116]

A fine-bore catheter may be introduced into the peritoneal cavity and fluid aspirated with or without lavage in order to detect pus or an abnormal number of leucocytes as a reflection of acute appendicitis. Unfortunately, two of the commonest conditions likely to be confused with acute appendicitis, namely gynaecological infections and mesenteric adenitis, may cause a leucocyte-rich exudate in the peritoneum. Gynaecological infections may also reveal pus on lavage. A negative lavage, however, usually excludes all three conditions. The presence of pus on lavage in a young male patient would exclude mesenteric adenitis. The presence of pus or a leucocyte-rich fluid in an elderly patient with right iliac fossa signs would suggest appendicitis, as both gynaecological infection and mesenteric adenitis are unlikely

Barium swallow

A single study[117] reports a 95 per cent accuracy in the diagnosis of acute appendicitis in children using this method. Filling of the appendix with barium excluded appendicitis. Non-filling plus a 'mass effect' on the caecum was highly suggestive of appendicitis.

Conclusions

Despite the panoply of sophisticated investigations reviewed above, there is no panacea for the diagnostic dilemma of acute appendicitis. No one test can reduce the rate of negative appendicectomy to zero. It should, however, be obvious that the usually accepted figure for negative appendicectomy of 15–30 per cent, based on unaided clinical diagnosis, is no longer acceptable. This figure can and must be reduced by ancillary measures.

Which one of the 11 different investigations should one choose and which can be rejected? A final answer cannot yet be given as there are no controlled clinical trials comparing them, but some conclusions can be drawn from the data at hand.

Plain radiography of the abdomen and the white cell count are highly inaccurate and should be discarded CT scanning is expensive, and inaccurate in the early case, and cannot be recommended for routine use. Diagnostic peritoneal lavage is attractive in its simplicity but has not been shown to be of value in the average case. Radioisotope scanning and barium swallow show promise but have not yet been adequately evaluated in large numbers of patients. Both are tainted by employing radiation. Scoring systems would appear to be ideal as they are accurate, non-invasive and require no special equipment, but further large-scale trials must be awaited. Laparoscopy is effective in reducing negative appendicectomy rates but its invasiveness makes one wary of promoting its widespread use. Barium enema is accurate and is readily available in most hospitals, but is vitiated by its radiation hazard Ultrasound examination is highly attractive but has a low sensitivity in some reports. Computer evaluation is marred only by requiring expensive equipment.

Thus four investigations remain whose value has been proved in clinical practice, namely laparoscopy, barium enema, ultrasonography and the use of computers. None has been proved to be better than any other of the remaining three, but each is indisputably better than no investigation at all. Which of the four is chosen depends in the first instance on what is available in the individual hospital. If there is a choice of which system to introduce into a department, a computer or ultrasound equipment is recommended. If none of the investigations are available, intensive in-hospital observation should be employed[8,26–30].

By using diagnostic aids for acute appendicitis, prolonged observation, negative laparotomies and the incidence of perforation can be reduced dramatically, resulting in decreased financial cost, which outweighs the cost of the systems employed.

A question arises concerning which patients should be investigated and which assessed purely clinically. The vast majority of the studies reviewed investigated only those patients where doubt existed about the diagnosis. A few, especially the computer studies, investigated all patients even when the decision to operate or not to operate was 'certain'. Some studies[80,90,104] have shown that even when the diagnosis of the acute abdomen is certain mistakes are still made, suggesting that all patients should be studied. Some authors[12,80] have recommended a combination of two or more investigations to increase accuracy even more.

In 1989, the 30 per cent safety margin surgeons allow themselves in the form of negative laparotomy in patients suspected of having acute appendicitis is no longer acceptable and has to be impugned. In the age of the silicone chip and the ultrasound wave, the X-ray beam and the endoscope, laparotomy can no more be used as a diagnostic procedure for appendicitis. The Gordian knot of appendicitis' diagnosis must not be untied with the scalpel.

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Endoscopic balloon dilatation of colonic anastomotic strictures

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Nine postoperative colonic and rectal strictures were treated using dilatation balloons passed over a guide-wire introduced endoscopically. Six strictures resolved after a single dilatation. The method is simple, safe, effective and avoids further surgery.

Keywords: Balloon dilatation, anastomotic stricture, rectum, colon

Colonic anastomotic strictures are usually secondary to ischaemia or leakage[1,2] (*Figure 1*). Following resections for carcinoma, some strictures will be due to recurrent disease[3]. The circular stapler may be responsible for an increase in the incidence of strictures compared with hand sewn anastomoses[4]. Most rectal and colonic strictures respond to simple dilatation but a few will be inaccessible and others fail to improve despite repeated dilatation. A further resection is technically demanding and may not be possible or advisable in all patients. We report a simple and effective method of stricture dilatation that avoids further surgery.

Patients and methods

From November 1983 to February 1987, nine patients with colonic anastomotic strictures shown on barium enema were referred for balloon dilatation (*Table 1*). Seven patients had symptoms of subacute large bowel obstruction while two were treated on the findings of a distal loop barium enema before closure of a defunctioning colostomy (*Figure 2*). All anastomoses had been hand sewn except for one reversal of Hartmann's procedure with a 31-mm EEA® stapler (US Surgical Corporation and Auto Suture UK, Ascot, UK) which had resulted in a stricture with a 3-mm lumen 5 months later.

Technique

After standard preadmission bowel preparation and sedation with 10–20 mg of intravenous Diazemuls® (KabiVitrum Ltd., Uxbridge, UK) plus 25–50 mg pethidine a flexible sigmoidoscope or colonoscope was passed to assess the stricture. Biopsies were taken if the original resection was for a carcinoma. A 0·038 inch (0·965 mm) guide-wire was passed, via the biopsy channel, through the stricture. The endoscope was then removed and a 20 mm (diameter) × 8 cm dilatation balloon (Medi-tech, Watertown, Massachusetts, USA) was passed over the guide-wire. The balloon was filled with dilute contrast and slowly dilated to 2 atm (202·6 kPa) using a pressure gauge under fluoroscopic control until the waisting at the stricture was abolished (*Figures 3* and *4*). Pressure was then maintained for 2 min.

After dilatation the anastomosis was inspected with the colonoscope. Most of the procedures were performed as day cases. Because of the small risk of colonic rupture the dilatation was performed in the morning and the patient was examined in the late afternoon to ensure that no complication had occurred. All patients were instructed to return immediately if they experienced any abdominal pain. One month later colonoscopy was repeated and a further dilatation performed if necessary.

Results

Six patients required only a single dilatation. Two patients required a second dilatation. One patient with terminal metastatic colonic cancer died 2 days after a third dilatation for palliation of pain from obstruction.

Follow-up of the eight surviving patients has been from 12 to 54 months (median 24 months) without recurrence of symptoms.

Discussion

A minor degree of anastomotic narrowing is common. The definition of a stenosis is variable in all series[4]. With bowel in continuity any stenosis that produces symptoms is a stricture

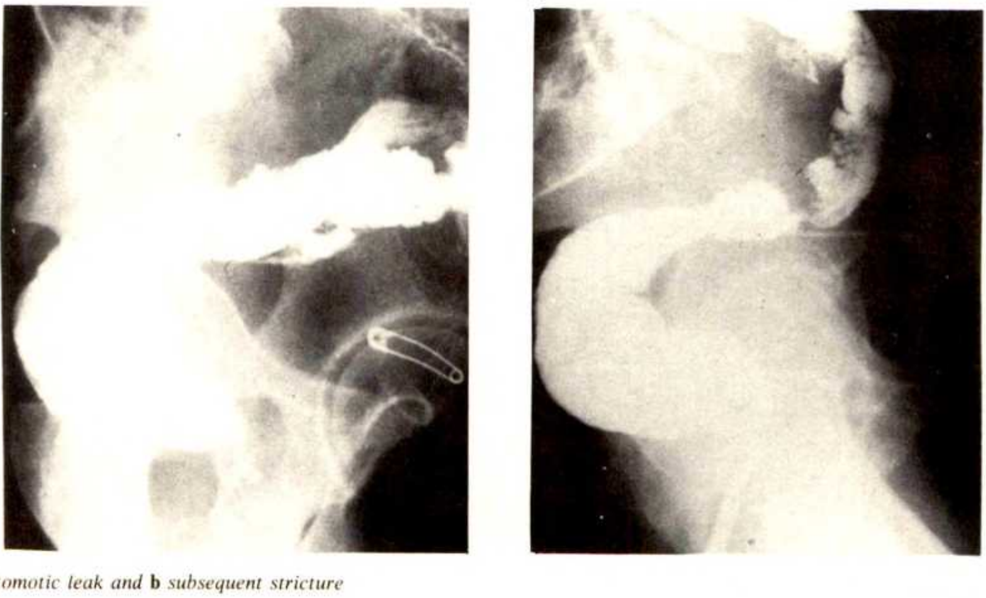

Figure 1 **a** *Anastomotic leak and* **b** *subsequent stricture*

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Table 1 *Details of nine patients with colonic anastomotic strictures*

Patient	Age (years)	Sex	Initial pathology	Original operation	Site of stricture (distance from anal margin)	Time of dilatation	Number of dilatations	Follow-up (months)
1	81	M	Crohn's(?)	Subtotal colectomy	Sigmoid (18 cm)	20 years after resection	1	23
2	60	M	Gangrenous sigmoid volvulus	Hartmann's procedure	Sigmoid (20 cm)	2 months after reversal of Hartmann's	1	25
3	64	M	Ischaemic colitis after aortic aneurysm repair	Anterior resection, transverse colostomy	Rectum (13 cm)	Before closure of colostomy	2	24
4	64	F	Adenocarcinoma (Dukes' A)	Anterior resection	Rectum (8 cm)	5 months after resection	2	26
5	21	M	Crohn's disease	Sigmoid colectomy, transverse colostomy	Sigmoid†	1 month after resection before closure of colostomy	1	54
6	51	F	Adenocarcinoma (obstruction)	Sigmoid colectomy, transverse colostomy	Sigmoid (16 cm)	4 months after closure of colostomy	1	24
7	79	F	Adenocarcinoma	Left hemicolectomy	Sigmoid (30 cm)	2 years after resection	1	12
8	57	M	Adenocarcinoma	Hartmann's procedure	Rectum (10 cm)	10 months after reversal of Hartmann's (stapled)	1	12
9	60	M	Adenocarcinoma	Sigmoid colectomy, transverse colostomy	Sigmoid (17 cm)	2 weeks after closure of colostomy	3	1*

* Patient died; † distance not measured in this patient

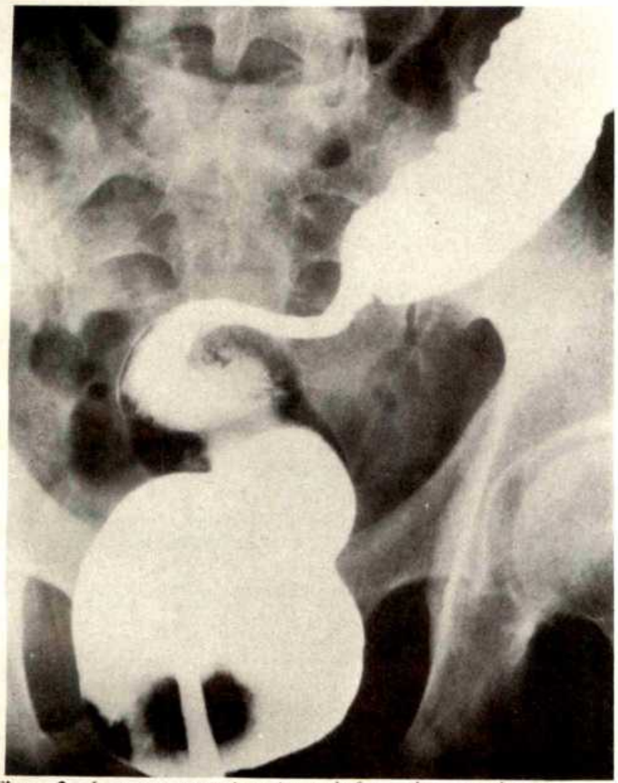

Figure 2 *Long anastomotic stricture before colostomy closure*

whatever the absolute diameter. In this series seven of nine patients had symptoms of large bowel obstruction. When a distal loop enema shows a stenosis the definition is more difficult as most will dilate spontaneously after colostomy closure. Probably only those that are very tight (less than 0·5 cm in diameter) should be dilated before colostomy closure, as with the other two patients in this study. All others should be reviewed regularly to check for the development of obstructive symptoms.

Many anastomotic stenoses will resolve over 6–12 months but a minority will cause persistent obstructive symptoms. In stapled colorectal anastomoses which developed strictures, transabdominal repair was required in 4·4 per cent[6]. Many methods of dilatation have been used. Digital dilatation may be suitable for some low rectal strictures. Sigmoidoscopes[7], Hegar dilators, Maloney's dilators[8] and stricturescopes[9] have been used. So have Eder–Puestow dilators[10] and Foley catheter balloons[11]. Gruntzig balloon catheters have been used in infants for dilatation of colonic strictures secondary to necrotizing enterocolitis[12]. Colonoscopy can be used to pass guidewires for Gruntzig-type balloon dilatation or the passage of Savary or Celestin dilators[13]. Recently transluminal partial excision of rectal strictures has been described, using a circular stapling gun after initial Hegar dilatation. The open gun is passed through the stricture and closed to excise a crescentic segment[14]. This has the potential risk of excising extrarectal tissue such as adherent small bowel or bladder and causing a fistula.

There is a single report of dilatation, using a guide-wire and a balloon, of an anastomotic stricture which may have been caused by postoperative radiotherapy[15]. Colonic Crohn's strictures have been successfully dilated endoscopically. One patient developed septicaemia soon after the dilation[16], so it may be advisable to use a single dose of prophylactic antibiotic for all balloon dilatations. For recurrent Crohn's disease at colonic anastomoses, and after anterior resection strictures that fail to respond to balloon dilatation, an endoscopic sphincterotomy has been used successfully[17].

Traditional push-type dilators (Maloney, Eder–Puestow, Savary) exert an axial shear force as well as a radial force. However, the operator does have a subjective sensation of the force required and of the tissue response. The theoretical advantage of balloon dilatation is that it only exerts a radial force and the maximal force is directed into the strictured segment. The fixed diameter of the balloon also ensures control over the extent of dilatation. The polymer material of the balloon is of low compliance and will rupture if expanded beyond its defined diameter[18,19]. As there is no tactile assessment of the completeness of dilatation the balloon must be filled with dilute contrast and viewed fluoroscopically. Dilatation should be slow to be safe.

If the stricture is very tight serial dilatation can be planned using a small balloon for the first dilatation and repeating the procedure with a larger one 1 month later.

Gruntzig-type balloon dilatation has been used successfully in the oesophagus, mainly for benign strictures[20,21] and achalasia[22]. There is little information on the benefits of balloon dilatation of malignant oesophageal strictures. The impression is that improvement is short-lived[21]. In our series one patient had skin metastases from his colonic carcinoma at the time of colostomy closure. The stricture had been secondary to an anastomotic leak (*Figure 1*). Biopsies of the anastomosis at colonoscopy did not show mucosal recurrence yet dilatation produced improvement which only lasted a few days. He died after a third dilatation that caused a pneumoperitoneum.

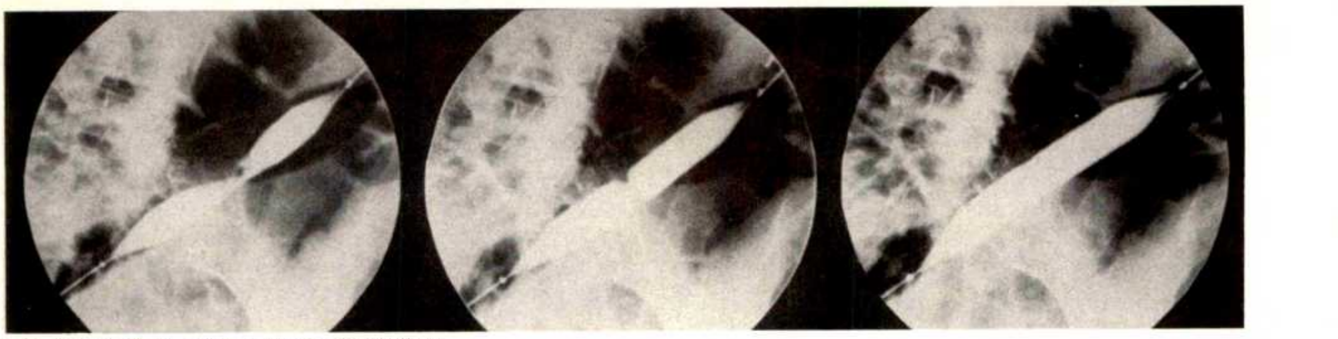

Figure 3 *Stages of dilatation; contrast filled balloon*

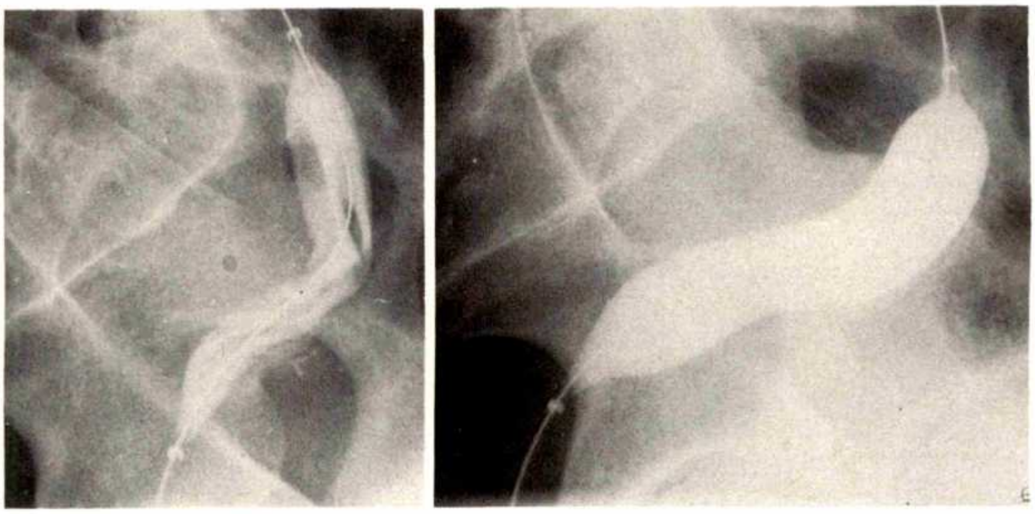

Figure 4 *Stages of dilatation of stricture in* Figure 1

Permission for a post mortem was refused but it is probable that recurrent tumour was present around the anastomosis. We would not recommend balloon dilatation for colonic strictures due to recurrent malignancy. Laser treatment is probably more effective if the recurrence is inoperable[23,24]. Neither would we recommend more than two dilatations of benign strictures if symptomatic improvement is not achieved or is transient. There should be 3 weeks or more between each dilatation provided that symptoms remain acceptable.

As endoscopic balloon dilatation is simple, successful and well tolerated it should be considered as the first treatment of symptomatic, benign, colonic anastomotic strictures.

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Effect of anterior resection on anal sphincter function

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Minor difficulties with continence may occur after low anterior resection. Intraoperative injury to the internal anal sphincter or its nerve supply may contribute to this. To study the effect of low anterior resection on the anal sphincter mechanism, anal manometry was performed on 20 patients before and 10 days after resection. Fifteen patients were studied again 6 months after operation. Resting, maximum squeeze and squeeze increment pressures were recorded. Intraoperative manometry ($n = 11$) *and presacral nerve stimulation* ($n = 6$) *were performed to determine whether peroperative injury to the internal anal sphincter had occurred. Resting and maximum squeeze anal canal pressures were reduced by low anterior resection, and did not recover. The squeeze pressure increment did not change. Division of the inferior mesenteric artery, full mobilization of the rectum and mesorectum, and rectal transection did not affect resting anal pressure, which was reduced after EEA® anastomosis* (*mean* (*s.e.m.*) *before, 40(5) mmHg; after, 27(4) mmHg;* $P < 0{\cdot}05$, $n = 5$). *Presacral nerve stimulation produced relaxation of the internal sphincter. Anal sphincter pressures are reduced after low anterior resection. The external anal sphincter and the nerve supply to the internal anal sphincter appear intact. A direct injury to the internal sphincter is postulated.*

Keywords: Rectal cancer, anterior resection, internal anal sphincter, external anal sphincter, continence

The rationale for sphincter-saving resection in patients with low rectal cancer is now widely accepted[1] and there has been a marked decline in the number of abdominoperineal resections performed[2,3].

Technical innovation, principally the introduction of circular stapling devices[4], has helped to overcome the difficulties of hand-sewn extraperitoneal colorectal anastomosis. With careful technique, a stapled extraperitoneal colorectal anastomosis appears to be as safe as a hand-sewn equivalent[5–7]. Thus the possibility of sphincter-saving resection is limited only by the need for adequate resection margins. Previously, a distal tumour-free clearance of at least 5 cm was widely recommended to minimize local recurrence. It is now clear that distal intramural and lymphatic spread is rare in rectal cancer, and a distal resection margin of 1·5–2·0 cm appears adequate in all but poorly differentiated and anaplastic tumours[1,8,9]. With this proviso, the long-term survival rates are similar for abdominoperineal resection and sphincter-saving resection[7,10].

While much attention has been paid to the cancer clearance aspects of sphincter-saving resection, the effect on the physiology of faecal continence has been less studied. The quality of life after rectal cancer excision is better in patients with sphincter preservation. However, 25–40 per cent of patients after sphincter-saving resection experience some difficulties with continence, particularly frequency and nocturnal leakage[11,12]. In the majority, stool frequency improves with time, associated with an increase in 'neorectal' capacity[13–18]. A similar phenomenon has been observed following ileal pouch–anal anastomosis for chronic ulcerative colitis[19]. While stool frequency after anastomosis appears to be a function of neorectal capacity and motility[20], impaired continence is probably related to anal sphincter injury[21].

Resting anal sphincter pressure is less in patients after sphincter-saving resection than in age-matched controls[13,22]. This observation could be explained by intraoperative injury to the sphincters or their nerve supply. This study was designed to investigate the effect of sphincter-saving resection on the anal sphincter mechanism and to determine whether intraoperative injury to the anal sphincter or its nerve supply could be detected

Patients and methods

Preoperative measurements

Twenty patients undergoing anterior resection were studied There were 11 men and 9 women of mean(s.e.m) age 64(3) years (range 34–79 years). Median tumour distance from the anal verge, measured at sigmoidoscopy, was 7 5 cm (range 5–12 cm). All anastomoses were extraperitoneal. Patients were admitted 2 days before operation and commenced on a standard bowel preparation. Preoperative anal manometry was performed on the day before operation, using a catheter, 5 mm in external diameter, perfused with saline at a rate of 0·5 ml/min and connected to a pressure transducer and a pen recorder Resting anal sphincter pressure was measured using a 1-cm station pull-through technique[23] and the maximum resting pressure was recorded. Patients were then requested to exert a maximum squeeze effort and the maximum squeeze pressure and the increment in pressure occurring with the squeeze effort was recorded at the same point in the anal canal. The rectoanal inhibitory reflex was tested by inflation of an intrarectal balloon with 50 ml of air while recording the resting anal canal pressure. A reproducible drop of 20 per cent of resting pressure was defined as a positive reflex. Patients were asked whether a sensation of rectal fullness was experienced during balloon inflation.

Intraoperative measurements

Of the 20 patients, 11 were included in the intraoperative study, seven men and four women of mean(s e m.) age 67(2) years. In addition to the measurements performed in the entire group of 20, this subgroup of 11 patients had additional measurements performed using different methodology. On the morning of the operation, benzodiazepine premedication was administered and both α-adrenergic and β-adrenergic blocking drugs were avoided In the anaesthetic room, before anaesthesia, a water-filled balloon constructed from the cuff of a modified Portex endotracheal tube[24], size 6·5, connected to a pressure transducer and pen recorder, was positioned in the midpoint of the anal canal and resting pressure was recorded. The manometry probe was held in position during the operation by suture to the perianal skin.

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A non-perfused, stationary balloon probe was chosen for intraoperative studies because of the ease of maintaining position and the difficulties associated with a perfused probe throughout a long operation. Furthermore, the diameter of a manometry probe is not critical to measurement of anal canal pressure[25] if the probe is left *in situ* for more than 15 min.

Anal canal pressure was measured before and after induction of anaesthesia and after division of the inferior mesenteric artery in all 11 patients Pressure was recorded in ten patients after full rectal mobilization and complete excision of the mesorectum[26], as is our standard practice, and in nine patients after rectal transection below the tumour. In five of these patients, anal resting pressure was recorded after completion of colorectal anastomosis using the 31-mm diameter EEA® stapler (US Surgical Corporation and Auto Suture UK, Ascot, UK) Any anal dilatation required to insert the instrument was achieved using the lubricated convex end of the instrument only The mean(s.e.m.) level of the anastomosis in these five patients was 4(2) cm.

Intraoperative presacral nerve stimulation

The presacral nerves are always identified and carefully preserved during mobilization of the rectum anterior to the fascia of Waldeyer as part of our standard procedure In six patients, while resting anal canal pressure was continuously measured, intraoperative presacral nerve stimulation was performed for 1 min using a bipolar nerve stimulator (Medelec MS 91, Woking, Surrey, UK) delivering square wave stimuli (duration 0·5 ms, frequency 20 pulses/min; amplitude 50 V)[27]. In four patients, presacral nerve stimulation was repeated after distal blockade of the nerve with 0·5 ml of 1 per cent Xylocaine (Astra Pharmaceuticals Ltd., King's Langley, UK).

Early postoperative measurements

Anal manometry was repeated using the same methodology, as for preoperative measurements, on all 20 patients on the day of hospital dismissal, usually the tenth postoperative day Anal canal resting pressure, maximum squeeze pressure and squeeze increment were measured. The rectoanal inhibitory reflex and the presence of rectal sensation were sought in the same manner as in the preoperative study

Late postoperative measurements

Anal manometry was repeated 6–12 months after operation in 15 patients. Of the original 20 patients, one had died, two had been given a protective transverse loop colostomy and were excluded, and two patients had been operated on <6 months before the time of most recent follow-up

Continence grading

Continence was graded from 1 (perfect) to 5 (requiring colostomy) as previously described[28].

Results

Preoperative and postoperative measurements

Resting and maximum squeeze anal canal pressures fell after operation and did not recover within 6 months The decrease in maximum squeeze pressure was not associated with a significant decrease in the squeeze pressure increment (*Table 1*). The rectoanal inhibitory reflex was present in 19 of 20 patients before operation, but was absent in 19 of 20 patients at discharge from hospital The reflex was identified in one of 15 patients ≥6 months after operation. The presence of the reflex in this case is probably explained by stimulation below the anastomosis. Rectal sensation, present in all patients before operation, was also present after operation.

Table 1 *Resting and maximum squeeze anal sphincter pressure and the pressure increment with squeeze effort in patients before and after low anterior resection and at follow-up ≥6 months after operation*

	Mean(s.e.m.) pressure (mmHg)		
	Preoperative ($n=20$)	Postoperative ($n=20$)	Follow-up ($n=15$)
Maximum resting pressure	67 (4)	51 (4)*	53 (5)*
Maximum squeeze pressure	103 (7)	78 (6)*	85 (7)*
Squeeze increment	35 (4)	27 (4)	31 (4)

* $P<0·01$ compared with preoperative value (paired Student's t test)

Table 2 *Intraoperative measurements of resting anal sphincter pressure in patients undergoing low anterior resection, compared with pre-anaesthetic measurements*

	n	Mean(s.e.m.) resting anal pressure (mmHg)	P*
Before anaesthetic	11	55 (6)	
After anaesthetic	11	36 (4)	<0·01
After inferior mesenteric artery division	11	33 (3)	n.s.
After mobilization	10	33 (4)	n.s.
After rectal division	9	33 (4)	n.s
After anastomosis	5	27 (4)	<0·05

* Paired Student's t test; n.s., not significant

Table 3 *Grading of continence in 15 patients ≥6 months after low anterior resection*

Grade	Description	n	
1	Perfect	12	87%
2	Incontinent of flatus	1	
3	Occasional minor soiling	1	
4	Frequent major soiling	0	
5	Incontinent (required colostomy)	1	

Intraoperative measurements

There was a significant drop in resting anal canal pressure measured in the anaesthetic room before induction and that measured following induction of anaesthesia (*Table 2*). Division of the inferior mesenteric artery at its origin, full mobilization of the rectum and mesorectum, and transection of the rectum did not affect the resting anal canal pressure (*Table 2*). Construction of a colorectal anastomosis by the EEA instrument inserted from below ($n=5$) was associated with a significant reduction in resting anal pressure (mean(s.e.m.) before anastomosis 40(5) mmHg; after anastomosis 27(4) mmHg; $P<0·05$). In each case, resting anal pressure fell after anastomosis.

Intraoperative nerve stimulation

Stimulation of the presacral nerves after rectal mobilization produced, in four of six patients, a transient inhibition of resting anal sphincter pressure (mean (s.e.m.) 10(2) mmHg). The inhibitory effect lasted 10–20 s, after which resting pressure slowly returned to prestimulation values, despite continued stimulation. The inhibitory effect was successfully blocked by infiltration of the presacral nerve with 0·5 per cent lignocaine distal to the point of stimulation.

Continence grading

The quality of faecal continence was recorded in 15 patients ≥6 months after operation (*Table 3*). Twelve patients considered that they had perfect continence. Two patients had faecal continence difficulties, the first requiring a permanent colostomy. This result, in a multipara, might have been predicted by preoperative manometry as the squeeze increment was only 10 mmHg. Intraoperative injury to the internal anal sphincter contributed to the poor outcome in the other patient in whom resting anal pressure fell from 40 mmHg preoperatively to 16 mmHg postoperatively and 18 mmHg at 6-month follow-up. In this case, a transient decrease in squeeze increment was also observed, but intermittent minor incontinence persisted after recovery of the squeeze increment to preoperative values.

Discussion

In health, faecal continence is maintained by a combination of the sphincteric and reservoir functions of the anal canal and rectum[29]. Other factors that contribute to continence are colonic motility, the anorectal angle and the volume and consistency of healthy stool. No single component of this complex arrangement appears to be all-important. However, functional reserve is obviously less if there has been impairment of sphincter function or reduction of reservoir capacity.

This study has concentrated on the effect of sphincter-saving resection on the anal sphincter component, and particularly on the internal sphincter component of the continence mechanism. After operation, both resting and maximum squeeze pressures in the anal canal were reduced. However, there was no reduction in pressure increment with squeeze effort, an observation which suggests that the effect of sphincter-saving resection is primarily on the internal anal sphincter. This effect may be permanent as 6–12 months after operation resting and maximum squeeze pressures are still reduced.

The mechanism of injury to the internal anal sphincter may be direct, or indirect to the innervation. The internal anal sphincter receives sympathetic motor innervation from the fifth lumbar segment of the sympathetic trunk which passes via the presacral nerves to the pelvic plexus. The parasympathetic motor supply comes from the second, third and fourth sacral nerves, which pass via the nervi erigentes to the pelvic plexus. Presacral mobilization of the rectum or division of the lateral ligaments of the rectum could interrupt either element of autonomic motor innervation[30]. The internal anal sphincter may also be supplied by myenteric nerves connected with the myenteric plexus of the distal colon and rectum[31]. The latter are influenced by sympathetic and parasympathetic nerves accompanying the inferior mesenteric artery and its branches. Division of the inferior mesenteric artery or transection of the rectum could alter mesenteric innervation of the internal sphincter.

Intraoperative recording of resting anal sphincter pressure was performed to elucidate whether injury to the nerve supply of the internal anal sphincter occurred during anterior resection. The results suggest that division of the inferior mesenteric artery, mobilization of the rectum anterior to the fascia of Waldeyer, and transection of the rectum have no effect on resting anal canal pressure. Indeed, stimulation of the presacral nerve following rectal mobilization produced an inhibitory effect in four of six patients. This effect, probably due to β-adrenergic inhibition of the internal anal sphincter[32], has been previously documented in patients undergoing resection or rectal mobilization for benign disease[27,33]. It is now shown to be preserved in at least some patients after rectal mobilization for cancer. Thus the sympathetic supply from the pelvic plexus to the internal sphincter does not run in the mesorectum. Failure to demonstrate inhibition in two patients may represent technical error or damage to the pelvic plexus. The resting pressures in these two patients were similar to those of others in the study.

Measurement of resting anal sphincter pressure after completion of the colorectal anastomosis using a transanal EEA stapler showed a significant reduction in pressure. This implies that insertion of the stapler, which we have noted sometimes requires significant dilatation, stretches the sphincter mechanism reducing resting pressure in the same manner as a Lord's procedure[34]. While this conclusion is at variance with a recent study, which showed no significant effect of controlled anal dilatation on resting anal pressures[35], a similar mechanism of injury has been suggested in patients undergoing ileal pouch–anal anastomosis with mucosal proctectomy during which considerable stretching of the anal sphincters occurs[21]. Indeed, use of an EEA stapler in patients undergoing ileoanal anastomosis without complete mucosal proctectomy is also associated with a fall in resting anal sphincter pressure, albeit less than that seen after complete mucosal proctectomy[36].

The clinical significance of reduced resting anal sphincter pressure after sphincter-saving resection is unclear. A number of investigators have documented a decrease in resting pressure in patients after anterior resection and coloanal anastomosis compared with age-matched controls[13,22,37]. A recent study examined 13 patients before and after low anterior resection and also documented a significant decrease in resting sphincter pressure[18]. However, none of these studies has shown a significant relationship with continence. By contrast, patients with impaired continence after ileal pouch–anal anastomosis have reduced resting anal canal pressure compared with continent patients and healthy controls[21]. It is probable that the larger volume of semisolid stool after ileoanal anastomosis places a greater strain on the continence mechanism than is present after resection. Thus damage to the internal anal sphincter is more likely to result in continence difficulties after ileoanal anastomosis than after resection.

The rectoanal inhibitory reflex was abolished in most patients in this study and did not return within 6 months. These findings are similar to those of Pedersen *et al.*[18], but contrast with other reports[13,14,16] in which the reflex was either preserved or seemed to return with time. Myenteric plexus regeneration across the anastomosis has been suggested as an explanation[14]. This is conceivable after hand-sewn anastomosis, but is unlikely after an inverted EEA stapled anastomosis. Absence of the anorectal inhibitory reflex did not appear to impair continence in this study.

Sphincter-saving low anterior resection has become the preferred surgical treatment in the majority of patients with carcinoma of the middle and lower thirds of the rectum. Preservation of continence while providing a safe and, where possible, curative procedure is the essence of this procedure.

We have shown that full mobilization of the rectum is possible without injury to the presacral innervation of the internal anal sphincter. Preoperative manometry should be considered in patients under consideration for sphincter-saving resection, particularly in multipara as internal sphincter damage caused by stretching, superimposed upon an already compromised external sphincter, may result in impaired continence.

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Announcement

Association of Surgeons in Training

Membership of the Association is open to all senior registrars holding accredited posts in general surgery, urology, plastic surgery, neurosurgery, orthopaedics, cardiothoracic surgery and paediatric surgery Registrars in the above specialties who are 2 years post-fellowship may also apply. The Association represents the views of members on all matters relevant to surgical training besides holding scientific and social meetings. If you are not a member please contact the Secretary, Andrew McIrvine, 35, Elsie Road, Dulwich, London SE22 8DX, for details of membership, local representatives and forthcoming meetings. The next AGM will be held in Cardiff from 21–23 September 1989: for information contact Mr B. J. Harrison, Department of Surgery, Cardiff Royal Infirmary, Newport Road, Cardiff CF2 1SZ, UK.

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Hypoplasia of defunctioned rectum

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The adaptive response of the large bowel to surgical defunction in man is essentially unknown, although in the rat there is progressive hypoplasia and a reduced propensity to experimental carcinogenesis. Mucosal biopsies were taken from the upper rectum completely defunctioned by a proximal stoma from 2 months to 5 years earlier in 11 patients and from 14 controls without abdominal operations or disease. Samples were established in organ culture and, after 16 h, crypt cell production rate (CCPR) was determined by a stathmokinetic technique. Crypt morphometry was also undertaken. CCPR in defunctioned large bowel was less than half that of controls: (mean (s.d.) 1·96 (0·68) versus 4·65 (0·54) cells crypt^{-1} h^{-1}, P<0·0001). Likewise, crypt length was 24 per cent lower (0·34 (0·05) versus 0·44 (0·04) mm, P<0·0001) and crypt width was 38 per cent lower (0·04 (0·01) versus 0·07 (0·01) mm, P<0·0001). Rectal defunction causes profound and persistent hypoplasia in man.

Keywords: Rectal hypoplasia, defunctioning colostomy, crypt cell proliferation rate

Temporary defunction of the large bowel, by proximal colostomy or ileostomy, is commonly performed to 'protect' a low anastomosis, to 'rest' the intestine in inflammatory bowel disease, and as an alternative to anastomosis in emergency procedures for colorectal obstruction and perforation Very little is known about cytokinetic changes in a defunctioned large bowel segment, although it is recognized that the blind loop of small bowel in patients with jejunoileal bypass probably undergoes atrophy and villous hypoplasia after exclusion from the luminal stream[1]. In man there is a single report of marked mucosal atrophy in a defunctioned rectum[2].

In the rat both the colon and the small intestine are as sensitive to surgical defunction as they are to withdrawal of food, undergoing progressive hypoplasia in each case[3,4]. Mucosal mass and crypt cell production rate (CCPR) in the left colon are halved within a month of proximal defunctioning colostomy[5-7], and crypt depth is reduced by 18 per cent in a colonic Thiry–Vella fistula[7] Colon atrophies rapidly during the first week of defunction and then at a slower rate for a further 3 weeks[5]. Bulk may be more important than nutrient content in maintaining colonic mucosal integrity, in this respect the colon differs from the small bowel[4,8] Low residue diets are antitropic, i e they diminish mucosal mass, even if caloric intake is kept constant[9]. Instillation of faeces into a colonic Thiry-Vella fistula partly restores normal mucosal mass[7].

In view of the close association between rates of colonic cell turnover and susceptibility to neoplasia[10], measuring parameters of adaptation in the human large bowel is becoming increasingly relevant to the understanding of colorectal carcinogenesis[11] In this study, CCPR and crypt size were used to assess adaptation in the defunctioned rectum of 11 patients. Results were compared with those in 14 controls.

Patients and methods

Eleven patients who had undergone defunction of the colorectum by proximal colostomy ($n=8$) or ileostomy ($n=3$) were studied Fourteen controls presenting to the outpatient department with no known colorectal (as opposed to anal) disease were also investigated The commonest diagnosis in controls was haemorrhoids (64 per cent); five patients had non-specific abdominal pain for which no cause could be found (*Table 1*) Eight (73 per cent) of those with a defunctioned rectum had undergone Hartmann's procedure (*Table 2*) In five of these diverticular disease was the underlying lesion (with a vesicocolic fistula) and three had had colonic carcinoma The remaining three patients had a defunctioning ileostomy for various indications. Patients and controls were of similar mean (s d) age (59·7 (13 8) *versus* 61 2 (17 1) years) and the sex distribution was roughly equivalent Defunction had been carried out 2–62 months before this study (median 4 months)

Biopsies

After fully informed consent was obtained, a sigmoidoscopy was carried out and two biopsies were taken from the upper rectum (or close to the blind end of the rectal stump) with Patterson® biopsy forceps (Downs Surgical Ltd , Sheffield, UK) Biopsies were then placed into ice-cold RPMI 1640® medium (Gibco, Paisley, UK) and were transported

Table 1 *Control subjects with a normal rectum*

Patient No.	Age (years)	Sex	Diagnosis
1	30	M	Haemorrhoids
2	62	M	Abdominal pain*
3	35	M	Haemorrhoids
4	67	F	Haemorrhoids
5	60	F	Haemorrhoids
6	75	M	Abdominal pain*
7	57	M	Abdominal pain*
8	77	F	Abdominal pain*
9	55	M	Haemorrhoids
10	75	F	Haemorrhoids
11	67	F	Haemorrhoids
12	66	M	Abdominal pain*
13	53	M	Haemorrhoids
14	57	F	Haemorrhoids

*Abdominal pain for which no clear cause was found

Table 2 *Patients with a defunctioned rectum*

Patient No	Age (years)	Sex	Operation/ diagnosis	Time since defunction (months)
1	65	M	Hartmann's (DD)	6
2	72	M	Hartmann's (Ca)	2
3	31	M	Crohn's*	24
4	57	F	Constipation*	22
5	27	F	Ulcerative colitis*	62
6	67	F	Hartmann's (DD)	7
7	71	F	Hartmann's (DD)	2
8	70	M	Hartmann's (Ca)	3
9	82	M	Hartmann's (DD)	3
10	62	F	Hartmann's (Ca)	2
11	69	M	Hartmann's (DD)	4

DD, diverticular disease, Ca, colorectal carcinoma, *patients with ileostomy

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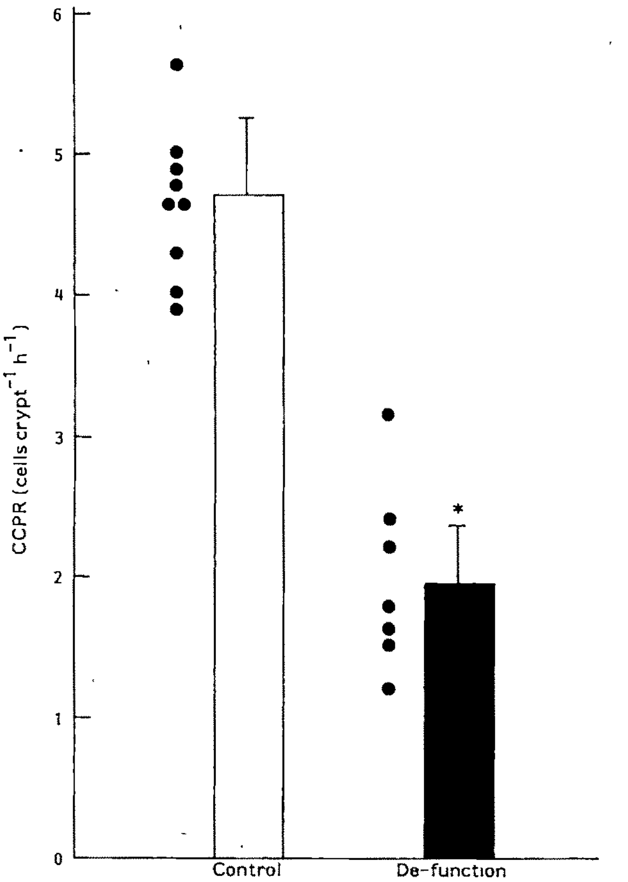

Figure 1 *Mean cell birth rates in rectal mucosa from control subjects (□, n = 9) and patients with colorectal defunction (■, n = 7); CCPR, crypt cell production rate; *, P <0·0001 (control* versus *defunctioned mucosa) The values for individual patients (●) and the standard deviations are shown*

to the organ culture laboratory. To avoid diurnal fluctuations in cell turnover rates[12,13], all sigmoidoscopies were performed in the early afternoon between 14.00 and 15.00 hours

Organ culture

Organ culture was carried out by the method of Trowell[14] modified by Allan and Jewell[15]. Rectal samples were oriented on a cork board and were divided into $2\,mm^2$ explants using a razor blade. Great care was taken to prevent samples drying by keeping them moist at all times Explants were placed mucosal surface uppermost on the triangular stainless steel grids of circular organ culture dishes. Each grid supported three to four explants. The organ culture medium was equilibrated with 95 per cent oxygen and 5 per cent carbon dioxide at 37°C for 1 h before use. Culture medium was RPMI 1640 (containing 25 mM Hepes buffer, 2 mM glutamine, 24 mM sodium bicarbonate) 90 per cent volume/volume, plus heat-inactivated fetal calf serum 10 per cent volume/volume Penicillin (100 units ml^{-1}) and gentamicin (40 μg ml^{-1}) were added to the final medium, which had a pH of 7·22–7·28 Medium was passed through a 0·22 μm millipore filter before being added to the central well of the dish. After adding medium (approximately 1 ml) the grid's surface was covered with fluid, but biopsies were not submerged. Cotton wool soaked in normal saline was placed in the outer well of the culture dishes to create a moist atmosphere Explants were then cultured in a gas-tight jar at 37°C in an atmosphere of 95 per cent oxygen and 5 per cent carbon dioxide

Stathmokinetic method

Our method of measuring cell proliferation in mucosal biopsies maintained in organ culture has recently been described[16] In brief, vincristine 0·5 μg ml^{-1} was added to the medium after 16 h culture Samples removed sequentially over the next 40–180 min were fixed in Carnoy's fluid for 4 h and then stored in 70 per cent alcohol Specimens were later stained by the Feulgen method for DNA, the muscle layer was stripped away and individual crypts were separated out under a dissecting microscope by microdissection[17]. The number of arrested metaphase figures in 15 crypts per sample was recorded, and the mean value was plotted against time after vincristine administration. The slope of the regression line so formed gives the CCPR in cells per crypt per hour (Reference 12).

Crypt morphometry

During microdissection the total length of 30 whole crypts per sample was measured by ocular micrometry. The crypt width was similarly measured at the mid-point along the length of the crypt.

Results

CCPR (Figure 1)

As previously seen[16], most samples were well preserved after 16–19 h of culture. It was impossible to measure CCPR in five controls (36 per cent) and four defunctioned patients (36 per cent) owing to unsatisfactory culture recognized by crypt necrosis. Among the remaining healthy biopsies, CCPR in seven patients with a defunctioned rectum was less than half that of the nine controls (mean (s d.) 1·96 (0·68) *versus* 4·65 (0·54) cells $crypt^{-1} h^{-1}$, $P<0.0001$). There was no correlation between CCPR and either age or length of time since defunction. There was no difference between counts obtained from crypts at the periphery of the specimens compared with those from the central regions. Indeed, if central necrosis was detected the specimens were discarded.

Crypt morphometry (Figure 2)

In patients with a defunctioned rectum, crypt length was 24 per cent less than that of controls and crypt width was 38 per cent less

Discussion

Striking morphological and cytokinetic changes occur in the human large bowel after defunction. As in animal experiments when sections of the large bowel are isolated from the luminal stream by proximal colostomy[6] or Thiry–Vella fistula[7], CCPR falls to less than half that of control values. Reduction in CCPR in man is sustained for at least 5 years after defunction. This persistent hypoplasia contrasts with the preliminary data reported by Winslet and colleagues[18], who found that 2 weeks after defunction CCPR was 35 per cent of initial values but by 12 weeks it had returned to normal. The present finding is in line with our own experimental work in rats[5–7].

The long-term reduction in CCPR found in two patients with ileostomies for inflammatory bowel disease is interesting as it provides an explanation for the mucosal recovery that can follow diversion of the faecal stream. Intact rectum in ulcerative proctitis shows increased CCPR whether the disease is in remission or relapse[19]. Carcinomas can still form in the defunctioned rectum in patients with ulcerative colitis[20] and in small bowel loops bypassed for Crohn's disease[21]. Perhaps in

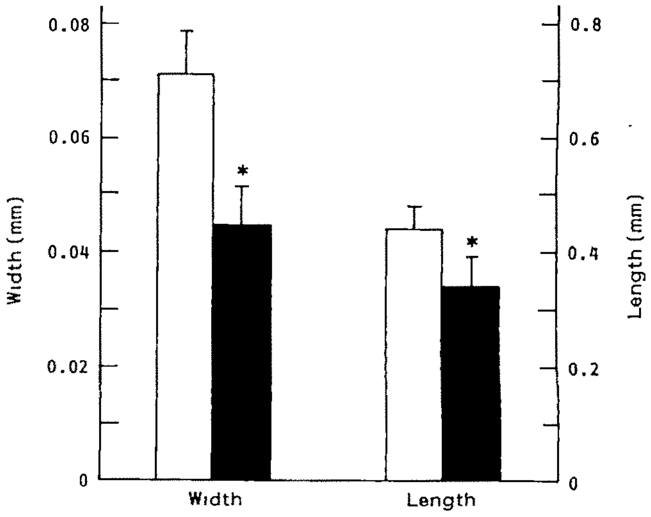

Figure 2 *Crypt morphometry in control (□) and defunctioned (■) rectal mucosa, * P <0·001 (control* versus *defunctioned mucosa). The mean and standard deviation are shown for crypt length and width*

such patients the co-carcinogenic stimulus of the underlying disease is so strong that it overcomes the antitropic effect of defunction, similar to the effect we have observed at a defunctioned anastomosis[22]. Alternatively, different mucosal kinetics may apply, possibly because of bacterial contamination.

Although morphometric parameters are not a very reliable index for quantifying adaptation[23], measurements made in microdissected crypts showed considerable crypt atrophy in defunctioned mucosa. Crypt morphometry has not previously been described in individual microdissected crypts. It is our subjective impression that the rectal stump is shrunken and atrophic after Hartmann's procedure, a finding that is strikingly apparent in the rat[6,7]. Mucosal hypoplasia is therefore involved in this process in man. The present study lends support to the single observation by Shaw-Dunn and Wright[2] of reduced mucosal (and muscularis) volume in the rectal stump excised 35 years after defunction for presumed ulcerative colitis. Thus large bowel excluded from the luminal stream behaves in a similar fashion to small bowel.

Although several patients with a defunctioned large bowel had had pathological processes (carcinoma, colitis) known to affect mucosal cytokinetics, such diseases are unlikely to have been the mediator of the 58 per cent fall in CCPR observed Cell birth rates in tumours are generally thought to be slower than those in normal epithelium[24], but two recent studies have shown that in patients with colorectal carcinoma or adenoma there is an increased rate of DNA synthesis throughout the whole colon, indicating a 'field change'[25,26]. Moreover, patients at high risk of developing cancer have wider proliferation zones in their colonic crypts ('phase 1' lesions)[11].

Organ culture studies in ulcerative proctocolitis nearly all show enhancement of CCPR[19,27] A recent study in Crohn's disease failed to show a raised CCPR, although the expected fall in CCPR after defunction did not occur[28]. It is likely, therefore, that the underlying disease process in the five patients with cancer or inflammatory bowel disease would tend to raise, rather than to lower, CCPR.

After colostomy closure in animals there is a rapid return to normal rates of cell turnover[5]. In man the process may take up to 3 months[28]. The high incidence of diarrhoea observed after colostomy closure may be due partly to the functional impairment that accompanies hypoplasia[7,29]. Functional adaptation of the colon is known to occur in rats, although evidence is scanty. Using a colonic perfusion model, Urban and colleagues[30] showed that net transport of electrolytes increases after enterectomy. This effect seems to be proportional to increases in mucosal cell mass rather than increased absorptive capacity of individual cells[30], and it is maximal in the caecum[31]. It might thus be expected that exclusion from the luminal stream would lead to a functional deficit. Conflicting reports abound concerning the correct timing of colostomy closure[29,32]. Early closure might reduce diarrhoea[29] but could conceivably promote metachronous carcinogenesis[33].

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Effect of nutritional supplementation on protein synthesis in tumour and host tissues of rats with colonic cancer

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Rats with colonic cancer were given a palatable liquid diet which enabled them to gain weight while those fed on stock diet, either ad libitum *or in restricted amounts, lost weight. Protein synthesis was measured* in vivo *using a flooding dose technique. Increased nutrient intake caused increases in the rate of protein synthesis in muscle, liver and non-diseased parts of the colon, but had no effect on protein synthesis in the tumours. These data suggest that enteral hyperalimentation may be safely employed in the preoperative management of patients with cancer, as it is likely to stimulate nitrogen retention in the host tissues without increasing the growth rate of the tumour.*

Keywords: Protein synthesis, cancer, nutritional support

Patients who are admitted to hospital for surgical treatment of gastrointestinal cancer are often malnourished[1,2]. Because malnutrition is believed to lead to increased risk of postoperative complications[3,4], it has been recommended that such patients should be given nutritional support for up to 2 weeks before the operation[5,6]. However, there is some concern that nutritional support may enhance the growth of the tumour[7]. It would clearly not be appropriate to give nutritional support if this was found to stimulate tumour growth more than repletion of host tissues.

One of the most prominent features of the malnutrition seen in cancer patients is wasting of skeletal muscle, and this has now been shown to be associated with a reduced rate of synthesis of muscle protein[8,9] Moreover, muscle represents up to 70 per cent of lean body mass, and changes in muscle protein synthesis are believed to be an important determinant of changes in protein metabolism in the body as a whole[10]. Thus, an increase in the rate of synthesis of muscle protein would be an early sign of reversal of the wasting process and hence an improvement in the patient's nutritional status.

We have made *in vivo* measurements of rates of protein synthesis in muscle and other tissues of rats with colorectal cancers. The rate of protein synthesis in the tumours has been measured to see whether they respond to increased nutrient intake. Nutritional supplementation was achieved by offering a liquid diet which was found to cause a spontaneous increase in food intake in these rats.

Materials and methods

Colorectal tumours were induced in female Wistar rats (Tuck and Son, Battlesbridge, UK) by repeated subcutaneous injections of dimethylhydrazine. The dose was 40 mg/kg body weight per week for 10 weeks and the method of preparation was that of Filipe[11] Signs of tumour presence, such as rectal bleeding, diarrhoea and abdominal distension, appeared after approximately 6 months.

Experiment 1

Eight symptomatic cancer bearing rats, of mean (s d) weight 315(5) g, were randomly allocated to receive either stock diet (41B*, BP Nutrition Ltd , Witham, UK), at a fixed rate of 10 g per day, or a liquid formula diet (Nutrauxil®, KabiVitrum, Stockholm, Sweden) fed *ad libitum*. Water was supplied to both groups *ad libitum* Rats were housed individually and food intake was measured each day for 7 days, after which protein synthesis rates were measured

Experiment 2

Eight symptomatic cancer bearing rats, of mean (s.d) weight 333(11) g, were randomly allocated to receive either stock diet (41B) or a liquid formula diet (Ensure®, Abbott Laboratories Ltd., Queenborough, UK) Both groups received food and water *ad libitum* Rats were housed individually and food intake was measured each day for 5 days, after which protein synthesis rates were measured.

Protein synthesis measurements

The method of Garlick *et al.*[12] was used to measure the rate of protein synthesis *in vivo* in the tumours, as well as in quadriceps and rectus abdominis muscles, in liver, and in parts of the colon not directly affected by tumour growth This involved injection of a flooding dose (150 μmol and 50 μCi (1·8 MBq) in 1 ml per 100 g body weight) of L-phenyl[2,3-^{3}H]alanine via a lateral tail vein, and killing the animals by decapitation 10 min later Tissues were rapidly cooled in iced water, removed, and stored frozen in liquid nitrogen. The fractional rate of protein synthesis was calculated from the ratio of specific radioactivities of free and protein bound phenylalanine measured by the specific, enzymatic assay

Statistics

Results were expressed as means with their standard errors, and statistical comparisons were made using Student's two-tailed t test for unpaired data.

Results

Weight gain and food intake (Tables 1 and 2)

Feeding the highly palatable liquid diets caused the rats to increase their intake of protein and energy above their *ad libitum* intake of conventional stock diet (experiment 2) as well as above the restricted intake of stock diet employed in experiment 1. This allowed the rats to gain weight, in contrast to both groups of stock diet fed rats which lost weight.

Table 1 *Weight gain and food intake of cancer bearing rats fed* ad libitum *on liquid diet (supplemented) or on a restricted amount of stock diet (control) for 7 days experiment 1*

	Supplemented ($n=4$)	Control ($n=4$)	P
Weight gain (g/day)	2·0(1·6)	−4·8(0·2)	<0·01
Energy intake (kcal/day)	95·0(3·6)	35·8	<0·01
Protein intake (g/day)	3·6(0·1)	1·3	<0·01

Values are mean (s e m); statistical analysis was by Student's t test

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Table 2 *Weight gain and food intake of cancer bearing rats fed* ad libitum *on liquid diet (supplemented) or on stock diet (control) for 5 days experiment 2*

	Supplemented (*n*=4)	Control (*n*=4)	*P*
Weight gain (g/day)	5·0(1 3)	−2·1(0·3)	<0 01
Energy intake (kcal/day)	100·5(6 7)	66 2(8 2)	<0 05
Protein intake (g/day)	3 8(0·3)	2·3(0·3)	<0·05

Values are mean (s e m); statistical analysis was by Student's *t* test

Table 3 *Fractional rates of protein synthesis in tissues of cancer bearing rats fed* ad libitum *on liquid diet (supplemented) or on a restricted amount of stock diet (control) for 7 days. experiment 1*

Tissue	Supplemented (*n*=4)	Control (*n*=4)	*P*
Quadriceps muscle	4 5(0·6)	3·7(0 8)	n.s
Rectus muscle	6·7(1·3)	3 0(0 3)	<0 05
Liver	86 9(4 9)	58 6(9 4)	<0·05
Colon	61 3(3 0)	33 4(3 4)	<0·01
Tumour	71 8(5 8)	83 9(12 9)	n.s

Values are mean (s.e.m.) per cent per day; n.s., not significant, statistical analysis was by Student's *t* test

Protein synthesis rates (Tables 3 and 4)

The rate of protein synthesis in two different skeletal muscles was increased by supplementary feeding in both experiments, although the difference did not quite reach statistical significance in the case of quadriceps in experiment 1. This suggests that the low rates of muscle protein synthesis which have been observed in human patients with cancer[9] may be at least partly caused by low food intake, and might be improved by increasing food intake.

Rates of protein synthesis in liver and colon were increased by supplementary feeding in experiment 1 but not in experiment 2. Apparently restriction of food intake in experiment 1 caused a reduction in the rates of protein synthesis in these tissues, and this was reversed by increasing the food intake.

In marked contrast to the effects on host tissues, supplementary feeding had no effect on the rate of protein synthesis in the tumours in either experiment. This suggests that protein synthesis for tumour growth was not limited by substrate supply, and indeed the tumours may already have been synthesizing protein at a maximal rate.

Discussion

Two different liquid diets were used in the two experiments in order to confirm that the effects observed were caused by increased nutrient intake rather than some qualitative aspect of the dietary supplement. Voluntary intake of both energy and protein reached approximately the same level in the supplemented animals in the two experiments, as did rates of tissue protein synthesis.

Reliable measurement of rates of tissue protein synthesis using isotopically labelled amino acids requires accurate measurement of the isotopic enrichment of the precursor pool as well as the protein product. This was achieved in the present experiments by injecting a flooding dose of tritiated phenylalanine[12]. The values we have determined for the rates of protein synthesis in colon, liver and muscle in nutritionally supported animals compare well with other published values for rats of this age[13–15]. Values for the rate of protein synthesis in colonic tumours in rats have not previously been reported.

Quadriceps and rectus abdominis muscles were chosen as representative of skeletal muscle in the body as a whole because they are both of mixed fibre-type composition and their response to malnutrition has been shown to be typical of that of hindlimb and trunk muscles respectively[16]. Interestingly, the difference in magnitude in protein synthesis rate between the two groups was slightly greater in the rectus abdominis than the quadriceps, and the data of Spence and Hansen-Smith[16] suggest that trunk muscles lose more protein in response to severe undernutrition than do limb muscles.

Table 4 *Fractional rates of protein synthesis in tissues of cancer bearing rats fed* ad libitum *on liquid diet (supplemented) or on stock diet (control) for 5 days experiment 2*

Tissue	Supplemented (*n*=7)	Control (*n*=7)	*P*
Quadriceps muscle	4·6(0·3)	3 1(0·3)	<0·05
Rectus muscle	5·1(0 2)	3·3(0 1)	<0 01
Liver	93·9(3 1)	95 4(4 7)	n.s
Colon	55·3(9·8)	46 6(7 4)	n s
Tumour	111(7)	110(7)	n s

Values are mean (s.e.m.) per cent per day; n s, not significant; statistical analysis was by Student's *t* test

It is known that food supply is an important factor regulating the rate of protein synthesis in muscle in the rat[17] and in man[10] under normal circumstances. We have previously shown that the rate of muscle protein synthesis in tumour bearing animals is reduced partly as a result of their low food intake[18]. The present results suggest that cancer does not prevent muscle, and indeed other tissues, from responding to increased nutrient intake with an increase in the rate of protein synthesis. We have, in fact, previously reported an increase in the rate of protein synthesis in muscle and in the whole body in patients with gastrointestinal malignancies who were given supplementary enteral nutritional support before operation[19]

An increase in protein synthesis would be expected to lead to improved maintenance of lean body mass Moreover, improvement in muscle mass, particularly of the respiratory muscles, could have a direct clinical benefit, as it has been suggested that wasting of the respiratory muscles, and the consequent inability to overcome respiratory infections, may be a very common cause of morbidity and mortality amongst cancer patients[9] It is known that muscle wasting caused by disease or malnutrition affects respiratory muscles to the same extent as other skeletal muscles[20]

Preoperative nutritional supplementation in patients with gastrointestinal cancers has been shown to reduce the subsequent incidence of wound infections[5], major complications and mortality[6]. In both these studies the nutrients were supplied intravenously and it has been argued that the clinical benefit which can be achieved is too small to justify the expense and the risk of catheter-related sepsis involved in such treatment The enteral route is a cheaper and less hazardous way of providing nutritional support and this should be equally beneficial for patients who retain a functioning gut. We have now shown that it is not likely to cause an unwanted stimulation of protein synthesis, and hence growth, in the tumour.

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Fatty tumours of the large intestine: a clinicopathological review of 13 cases

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Thirteen cases of benign fatty tumours of the colon have been reviewed. There were ten instances of submucosal lipoma, two of which were multiple, and three of lipohyperplasia of the ileocaecal valve. Abdominal pain and gastrointestinal bleeding were the commonest symptoms. Barium enema and angiography were misleading, the former in confusing polypoid lipomas and protruberant ileocaecal valves with carcinoma, the latter in misinterpreting fatty tissue vasculature as angiodysplasia in three patients. Most lesions were in the right side of the colon, and many were treated by limited colectomy as if for carcinoma or angiodysplasia. No patient has died as a result of their disease. Awareness of the possibility of colonic lipomas and knowledge of the normal ileocaecal valve anatomy are of importance to radiologists and endoscopists, particularly now that angiography is localizing the smaller fatty lesions.

Keywords: Lipoma, large intestine, ileocaecal valve

Although lipomatous lesions are the second commonest benign tumour of the large bowel, they are relatively uncommon in clinical practice. With the advent of colonoscopy and selective angiography the type of fatty lesion resected is changing. In this review we document our experience.

Patients

A review of the surgical pathology files at the Institute of Pathology at the London Hospital over a 50-year period revealed 13 cases of fatty lesions in the large intestine (*Table 1*). Nine of these were resected in the 10-year period up to 1987. There were eight women and five men, and their ages ranged from 35 to 78 years, with a mean of 59 years.

Investigations included barium enema (seven cases) and colonoscopy (seven cases), with selective superior mesenteric angiography (*Figure 1*) performed in three (cases 9, 10, 12). The preoperative diagnoses recorded included carcinoma of the colon in five, angiodysplasia or other vascular malformation in three and one intussusception of unknown cause.

Eight patients underwent a limited colectomy, while the remaining five cases had removal of the nodule with the overlying mucosa.

The histological diagnosis was submucosal lipoma in ten (five men, five women, mean age 53 years) and lipohyperplasia of the ileocaecal valve in three cases (all women, mean age 73 years).

We describe one patient (case 12 in *Table 1*) in detail to illustrate the problems in diagnosis of gastrointestinal blood loss. This woman had a Starr–Edwards aortic valve replacement for aortic valve disease in 1977 at the age of 57 years and was put on long term anticoagulation therapy. In 1982 after some melaena a diagnosis of duodenal ulcer was made. She had further melaena and in 1987 a diagnosis of caecal angiodysplasia was made following selective superior mesenteric angiography. After two unsuccessful attempts at colonoscopic cauterization of the lesion she underwent a right hemicolectomy. Pathological examination showed lipohyperplasia of the ileocaecal valve with many ectatic blood vessels in the adipose tissue and overlying mucosa but no ulceration or apparent site of blood loss into the bowel. Her melaena persisted and gastroduodenoscopy showed a small duodenal erosion which was cauterized. It was decided to replace the Starr–Edwards aortic valve with a xenograft so that the patient could come off warfarin. In late 1987 a Carpentier–Edwards bioprosthesis was inserted. Subsequently she has remained well with no further blood loss from the gastrointestinal tract.

Results

On macroscopic examination the submucosal lipomas had a lobulated yellow-white appearance, and most were greater than 2 cm in diameter. In these larger ones, particularly those associated with an intussusception (*Figure 2*), there were varying degrees of necrosis. Many of the larger lipomas were polypoid, with ulceration of the overlying mucosa. Microscopically there was normal adipose tissue, with fat necrosis and granulation tissue in the larger intussuscepted and traumatized cases. Postresection angiography was performed on two of the specimens where angiodysplasia was suspected. Ectatic blood vessels within the fatty tissue were seen in some, but in none was a site of blood loss identified.

All three patients with lipohyperplasia of the ileocaecal valve showed thickening and pouting of the valve which protruded into the caecum (*Figure 3*). Angiography was performed on the resected specimen in case 12 where angiodysplasia was suspected. Microscopically there was excessive fatty tissue in the submucosa, with ectatic blood vessels distributed through it and extending up to the mucosa. There was no ulceration. No other sites of bleeding or of angiodysplasia were demonstrated in the resected specimens.

Discussion

Lipomas of the large bowel were initially described by Bauer in 1757[2,3], although it was not until 1909 that Stetten[4] emphasized that they can clinically mimic colonic carcinoma. In 1985 Hall *et al.*[1] using case 9 illustrated how they can mimic angiodysplasia.

The incidence of lipoma of the colon has been reported from autopsy series to range from 0·035 to 4·4 per cent[5,6]. Mayo *et al.*[7] reviewed surgical material exclusively: out of 4000 cases of benign neoplasms of the gastrointestinal tract they found 164 (4 per cent) lipomas. Most involved the ileocaecal valve and large bowel; the stomach and proximal small bowel were less commonly affected.

The size of the lipoma is important[2,6–10], and only those over 2 cm, as were most of those in our series, produce symptoms. The commonest symptoms were bleeding per rectum and abdominal pain, similar to the reported findings. The rectal bleeding was in general related to the smaller lesions, whereas abdominal pain was related to episodes of intussusception or intestinal obstruction associated with the larger, frequently polypoid lipomas. Lipomas of the colon have usually been reported to be from 1·5 to 2 times more common in women[10].

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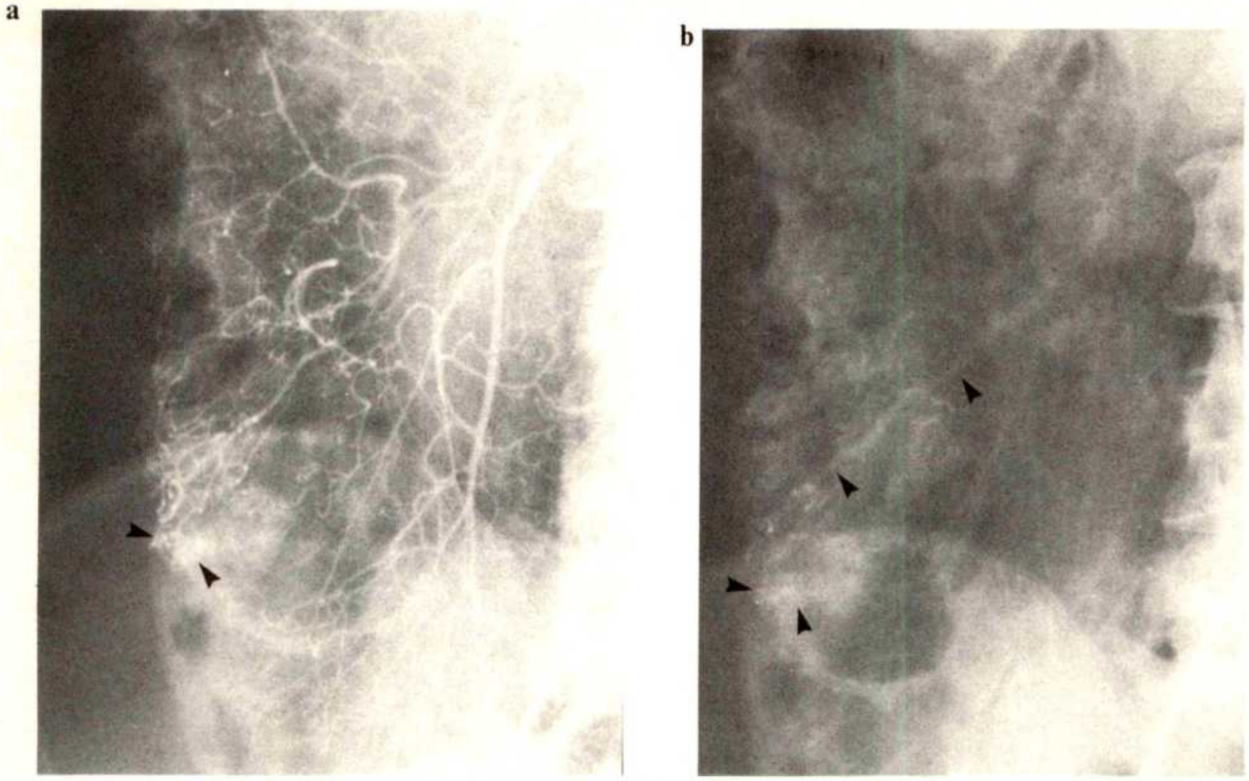

Figure 1 *Case 10: ileocaecal lipohyperplasia. Angiogram showing vascular lesion in the caecum;* **a** *arterial phase and* **b** *venous phase*

Table 1 *Clinical and pathological details of fatty tumours of the large intestine*

Case	Age (years)	Sex	Symptoms	Site	Size (cm)	Pathology
1	50	M	Abdominal pain	Transverse colon	4·5 × 4 × 3	Submucosal lipoma
2	53	F	Not known	Hepatic flexure	5 × 3·5 × 3	Submucosal lipoma
3	44	M	Abdominal pain	Ascending colon	3 × 3 × 3	Submucosal lipoma
4	50	F	Abdominal pain	Hepatic flexure	7 × 4 × 4	Submucosal lipoma
5	?	F	Bleeding per rectum for 3 months	Sigmoid colon	4 × 2 × 1	Submucosal lipoma
6	?	M	Not known	Caecum	6 × 4 × 3·5	Submucosal lipoma
7	60	M	Diarrhoea and bleeding per rectum	Sigmoid colon	7 × 3 × 3	Submucosal lipoma
8	35	M	Anaemia	Caecum	1 × 0·5 × 0·5	Submucosal lipomas
9*	71	F	Bleeding per rectum for 18 months	Caecum	1 × 1 × 1 (multiple)	Submucosal lipomas
10	63	F	Gastrointestinal bleeding for 3 years	Caecum	1 × 1 × 1	Submucosal lipoma
11	78	F	Pain on defecation	Ileocaecal valve	2 × 2 × 2	Lipohyperplasia
12	67	F	Bleeding per rectum	Ileocaecal valve	2.5 × 2·5 × 2	Lipohyperplasia
13	74	F	Watery diarrhoea	Ileocaecal valve	2 × 2 × 2	Lipohyperplasia

* Reference 1

Lipomas of the large bowel may be submucosal, subserosal or intermucosal–serosal. In the literature the first type is commonest (90 per cent of large bowel lipomas) and this too is our experience. The most common site is the right side of the colon.

Many lipomas in this series were removed because they were suspected of being carcinomas. Differentiation between the two may be difficult but is important as the surgical management differs considerably. In general, weight loss and anorexia are associated with carcinoma. Lipomas tend to be located on the right side whereas there is a left-sided predeliction for epithelial neoplasms[11]. Radiological differentiation between the two is difficult, but fatty tumours are radiolucent which may be helpful. Ginzberg *et al.*[12] noted some features which they considered diagnostic: a round or ovoid, lucent, filling defect with smooth margins, frequently lobulated, especially in the right colon. Barium enema studies may demonstrate a mass that changes size and shape (squeeze sign) throughout the examination due to peristaltic bowel movements[13]. Water enemas have been advocated[14,15] to improve the contrast with the radiolucent fat. Computerized tomography is considered by some to be the definitive diagnostic measure in recognizing colonic lipomas[16,17].

Colonoscopy may allow direct visualization of the submucosal lipoma, which may be easily indented with a closed biopsy forceps. The tumour will rapidly spring back to resume its previous shape on withdrawal of the forceps (pillow or cushion sign). Pressure on the lipoma will compress the

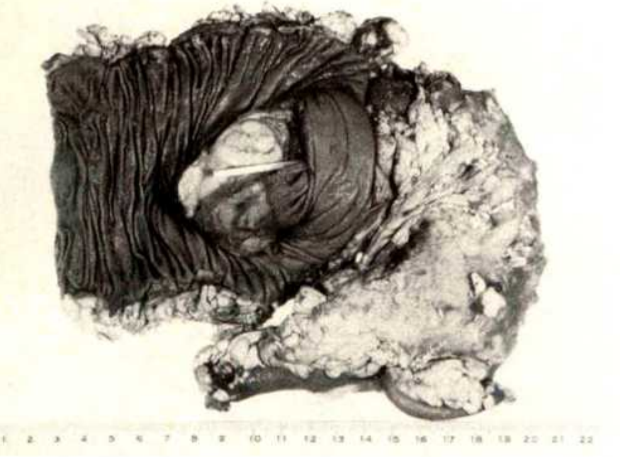

Figure 2 *Case 3 showing colonic intussusception, with white stick marking the lipoma*

overlying superficial vessels to disclose the characteristic yellow coloration of lipid. The mucosa may be grasped with the forceps and pulled up, lifting it like a tent away from the lipoma. If the surface mucosa is removed from one site by repeated biopsy from the same location (well technique), fat may be seen protruding from the biopsy site. This 'naked fat sign' is considered pathognomonic of a lipoma[18]. While colonoscopy is reliable for the diagnosis of the usual lipoma, when the lesion is atypical, firm or ulcerated it is more difficult.

In two of our cases (cases 8 and 9) the diagnosis was multiple lipoma. The incidence of multiple lipoma varies in the reported series. Haller and Roberts[2] found only 20 cases reported in the literature up to 1963, although Castro and Stearns[8] found 11 patients (24·4 per cent) in their review of their own material. Khawaja[19] states that in 10 per cent of cases lipomas are multiple.

The management of symptomatic colonic lipomas is dependent on their size and location, with consideration given to the possibility of intussusception if left untreated. Treatment varies from hemicolectomy to segmental resection to local excision, but much is dependent on the correct preoperative diagnosis and the intraoperative findings. Colonoscopic removal of polypoid submucosal lipomas is an established safe method of treatment[20], although in very large lesions the pedicle or stalk may actually be formed by serosal invagination. Snaring and cutting of such a stalk would result in free perforation[19].

The spontaneous expulsion of a lipoma per rectum has been recorded[21], in association with both colonic intussusception[3] and colonic perforation[22].

The aetiology of colonic lipomas is not known. They are usually found in the older patient, but no association has been recorded with diabetes, hyperlipidaemia or other degenerative diseases. An association between Weber–Christian disease and colonic lipomas has been reported[23].

The ileocaecal valve syndrome, where patients have symptoms of bloating, right-sided abdominal pain, and tenderness over the site of the ileocaecal valve, is said to be due to hypertrophy of the ileocaecal sphincter which pouts into the caecum[24]. This may be demonstrable on barium enema examination. Lipomas have been demonstrated on the caecal side of the valve[24]. Three of our cases showed this protrusion of the valve, a feature noted occasionally by endoscopists. The preoperative diagnoses were carcinoma and angiodysplasia. Microscopy showed lipohyperplasia, a diffuse increase in adipose tissue in the submucosa of the valve[25]. Whether this feature is a variation of the normal anatomy of the ileocaecal valve, or deserves the designation lipohyperplasia, is open to question. Haller and Roberts[2] discussed fatty infiltration of the ileocaecal valve, and their Figure 1 demonstrates the difference between a lipoma of the ileocaecal valve and an ileocaecal valve with increased adipose tissue. The presence of a limiting membrane in the former is the mainstay of differentiation between the two. They do not use the term lipohyperplasia. None of our cases was very well circumscribed with a limiting membrane. Lipohyperplasia of the ileocaecal valve is usually a localized manifestation of generalized obesity, although none of our patients was overweight.

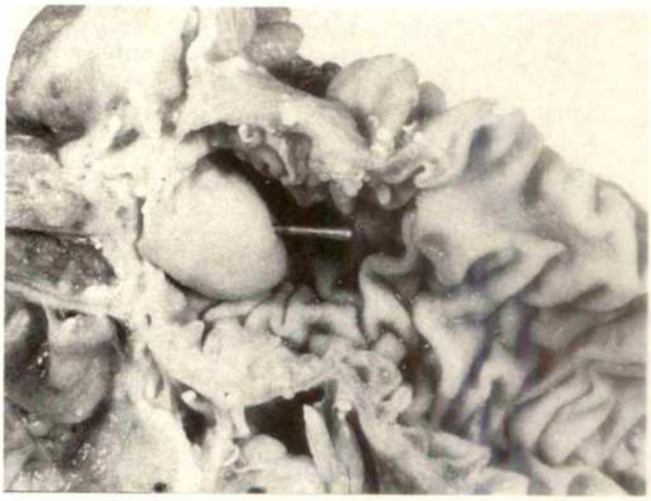

Figure 3 *Case 12: resected specimen with a probe in the bowel lumen*

The ileocolonic junction acts both as a mechanical valve and a functional sphincter[26] and has been studied *in vivo* through a caecostomy[27] and by endoscopic observations[28]. It varies from a labial (flat) form to a papillary form depending on the kinetic state of the bowel. Mimicry of a malignant tumour has been recorded[29].

Case 12 is interesting because of the association of gastrointestinal bleeding with aortic valve disease[30]. The association may be spurious and due to the anticoagulant therapy.

It is notable that in our experience the more recently diagnosed fatty lesions of the colon have been smaller than those previously removed, and they have been picked up by selective angiography. Whether they were the true cause of the rectal bleeding is open to question; however, the recognition of fatty lesions, and their distinction both from angiodysplasia and the variations of anatomy of the ileocaecal valve must be recognized. The radiological criteria for the angiographic diagnosis of angiodysplasia must be rigorously followed[31]. The fact that angiodysplasia most commonly occurs in the caecum makes the radiological distinction between that and the normal or abnormal ileocaecal valve difficult.

Acknowledgements

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Case report

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Toxic megacolon and perforation caused by Salmonella

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Case report

A 41-year-old man was admitted to hospital with a 2-week history of bloody diarrhoea, 10–15 episodes daily. For the previous year he had had numerous similar but less severe episodes. On admission vital signs were normal and the abdomen was soft and non-tender with normal bowel sounds. Stools were positive for occult blood. Stool samples were sent for culture. Twenty-four hours after admission he developed severe abdominal pain and became pyrexic (39°C). An abdominal X-ray showed gross dilatation of the transverse colon and free gas in the peritoneal cavity. Blood cultures were taken; he was commenced on intravenous antibiotics and transferred to the surgical department at our hospital. On admission he was pyrexic (39°C) and his pulse and blood pressure were normal. His abdomen was rigid and silent. Initial investigations showed haemoglobin 9·0 g/dl, white cell count $5 \cdot 4 \times 10^9$/litre, serum albumin 25 g/l, and normal urea and electrolyte concentrations. He was taken to theatre shortly after admission where sigmoidoscopy before laparotomy showed normal-looking rectal mucosa. At laparotomy there was free gas and mild peritoneal contamination.

There were numerous perforations in the transverse colon which was very friable. The ascending and descending colon were diseased to a lesser extent while the lower sigmoid colon and rectum looked normal. The small intestine was normal.

A subtotal colectomy, leaving the sigmoid colon and the rectum, was carried out and an ileostomy and mucous fistula were fashioned. His postoperative course was uneventful. Blood and stool cultures showed *Salmonella Newport* as did the peritoneal fluid taken at the time of laparotomy.

Histology of the resected colon showed severe colitis, possibly ulcerative colitis or Crohn's disease, but consistent with a *Salmonella* colitis.

At outpatient review 2 months postoperatively he was very well; *S. Newport* was grown from ileostomy effluent and rectal biopsy showed normal mucosa. Bowel continuity was restored 3 months after operation and he is well and asymptomatic 2 years later.

Discussion

A small number of colonic perforations due to *Salmonella* have been reported, almost all in association with small bowel perforations[1,2]. This is the first report of colonic perforation caused by *S. Newport*. Although the small intestine is regarded as the principal site affected by *Salmonella* infection, it has been suggested that colonic involvement is frequent and is probably important as a cause of the diarrhoea[3]. Differentiation between *Salmonella* colitis and ulcerative colitis can be difficult as: (1) sigmoidoscopic findings may be identical; (2) toxic dilatation of the colon can occur in both conditions; (3) histological examination in salmonellosis may show florid crypt abscesses and other changes similar to those found in idiopathic ulcerative colitis[4]; (4) *Salmonella* infection can occur in association with ulcerative colitis[5].

In our patient the provisional diagnosis at the time of admission was ulcerative colitis. Because the rectum was normal on sigmoidoscopy and at laparotomy, Crohn's disease was then considered. It should be noted that the rectum is not usually spared in *Salmonella* colitis[3].

This case report shows that not all cases of toxic megacolon are due to inflammatory bowel disease and in the acute situation, when presented with a perforated toxic megacolon in a patient with a history very suggestive of ulcerative colitis, the rectum should be retained.

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Collagen changes around intestinal anastomoses in germ-free rats

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The changes in collagen, measured as hydroxyproline, concentration around both ileal and colonic anastomoses in germ-free and control rats have been investigated and compared with each other. The germ-free rats were raised, operated on and maintained under completely pyrogen-free conditions. Animals were killed 2, 3 or 7 days after operation. There was a significant reduction in the lowering of hydroxyproline concentrations around the colonic anastomosis of germ-free rats compared with control rats both in the anastomosis at days 2 and 3 (P = 0·04 and P = 0·006 respectively) and in the proximal segment at day 3 (P = 0·03). In ileal anastomoses, significant differences between control and germ-free rats were only found at 7 days. Here, the increase in hydroxyproline concentration observed in control rats was significantly reduced in germ-free rats. These data are taken to support the hypothesis that bacteria affect colonic anastomotic healing by contributing to postoperative collagen degradation.

Keywords: Germ-free rats, collagen, intestinal anastomosis, wound healing

Dehiscence of large bowel anastomoses is a frequent complication in colonic surgery and is associated with a considerable mortality rate[1]. On the other hand, the leakage rate of ileal anastomoses is low[2]. In order to devise measures to prevent dehiscence, the crucial steps in anastomotic healing should be defined. Comparison of the healing sequence in small and large bowel might be helpful in this respect.

The structural protein collagen is of major importance in maintaining the strength of the intestinal wall. Investigations into the healing of intestinal anastomoses in various animals have shown that massive changes in collagen concentrations occur during the first week after operation[3–5], changes which are more extensive in the colon than in the ileum[6,7]. It is generally believed that immediately after operation collagen degradation occurs, followed by *de novo* synthesis. This 'collagenous equilibrium' is thought to be of paramount importance in undisturbed healing[8].

An obvious difference between small and large bowel is the increased presence of micro-organisms in the latter. As bacteria are capable of producing collagenolytic enzymes[9], they might enhance postoperative collagen degradation and consequently affect anastomotic healing. Thus, it is of interest to examine the behaviour of collagen under conditions where bacteria are completely absent during operation and subsequent healing.

For this purpose, we have compared changes in collagen concentrations around intestinal anastomoses in germ-free rats with those found in normal rats.

Materials and methods

Animals

Two groups of male Wistar rats were used: 30 control rats (average weight 244 g) and 45 germ-free rats of similar age and weight. They were fed a standard diet (Hope Farms, Woerden, The Netherlands) and allowed water *ad libitum*.

The germ-free rats were born and raised under sterile conditions[10]. Immediately before operation the animals were moved, taking full precautions against bacterial contamination, from quarantine to a cage in a horizontal laminar flow workstation, where the operation was performed under pyrogen-free conditions. The animals remained in the same place until they were killed. Before operation and before killing the rats, faecal samples were taken for culture. All preoperative samples were negative. However, 20 of the 45 faecal samples taken before killing the rats showed bacterial contamination. These animals were excluded from the series. Thus 25 germ-free rats remained which were killed 2 ($n = 7$), 3 ($n = 11$) and 7 ($n = 7$) days after operation. The three comparable control groups, operated on under non-sterile conditions, consisted of ten animals each.

Operative procedure

Operations were performed as described previously[11]. Briefly, anaesthesia was induced with sodium pentobarbital, a median laparotomy was performed and 1 cm of both the ileum and the colon were resected at 15 cm proximal to the ileocaecal junction and 3 cm proximal to the rectal peritoneal reflection respectively. An inverting one-layer end-to-end anastomosis was constructed using a microsurgical technique. After 2, 3 or 7 days the rats were killed by an intracardiac overdose of sodium pentobarbital. Both anastomoses were dissected out and cleaned from surrounding tissue. Three 1-cm samples were collected, one containing the anastomosis in the middle and the others comprising the adjacent proximal and distal segments. These postoperative sections of bowel were compared with the control segment removed during operation. In this way each animal served as its own control.

All samples were frozen immediately and stored in liquid nitrogen until further processing.

Analytical procedures

The samples were pulverized in liquid nitrogen, lyophilized, weighed and kept at −30°C for analysis. In all samples the hydroxyproline content, as a reflection of the collagen level, was measured as described previously and essentially according to the method of Prockop and Udenfriend[12]. Total protein was assayed by the Lowry method[13], using bovine serum albumin as a standard. Statistical methods employed are mentioned with the results.

Results

The hydroxyproline concentrations in uninjured intestine, as represented by the control segments removed at operation, are shown in *Table 1*. Concentrations were always higher in the colon than in the ileum. While hydroxyproline levels were significantly higher in the ileum of germ-free rats than in control rats, the colon of germ-free rats contained significantly less hydroxyproline than the colon of control rats.

Construction of an anastomosis strongly affects hydroxyproline concentrations around the operative area, both in the ileum (*Figure 1*) and in the colon (*Figure 2*). In control rats, the postoperative decrease in hydroxyproline levels was most

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Table 1 *Hydroxyproline concentrations in control segments*

	Days on which rats killed	*n*	Hydroxyproline concentrations: Ileum	Hydroxyproline concentrations: Colon
Control rats	2	10	7·3 (1·7)	15·3 (2·6)
	3	10	7·5 (1·9)	16·2 (3·9)
	7	10	7·2 (1·4)	15·4 (1·8)
Total		30	7·4 (1·6)	15·7 (2·8)
Germ-free rats	2	7	9·3 (2·1)	12·9 (2·9)
	3	11	7·9 (0·9)	12·1 (1·8)
	7	7	9·3 (0·9)	15·0 (1·9)
Total		25	8·7 (1·5)	13·1 (2·5)
Control *versus* germ-free			$P=0{\cdot}0045$	$P=0{\cdot}0015$

Results are expressed as mean (s.d.) in micrograms per milligram dry weight. The levels of significance for the differences observed between germ-free and control rats are calculated by the Kruskal–Wallis K-sample test

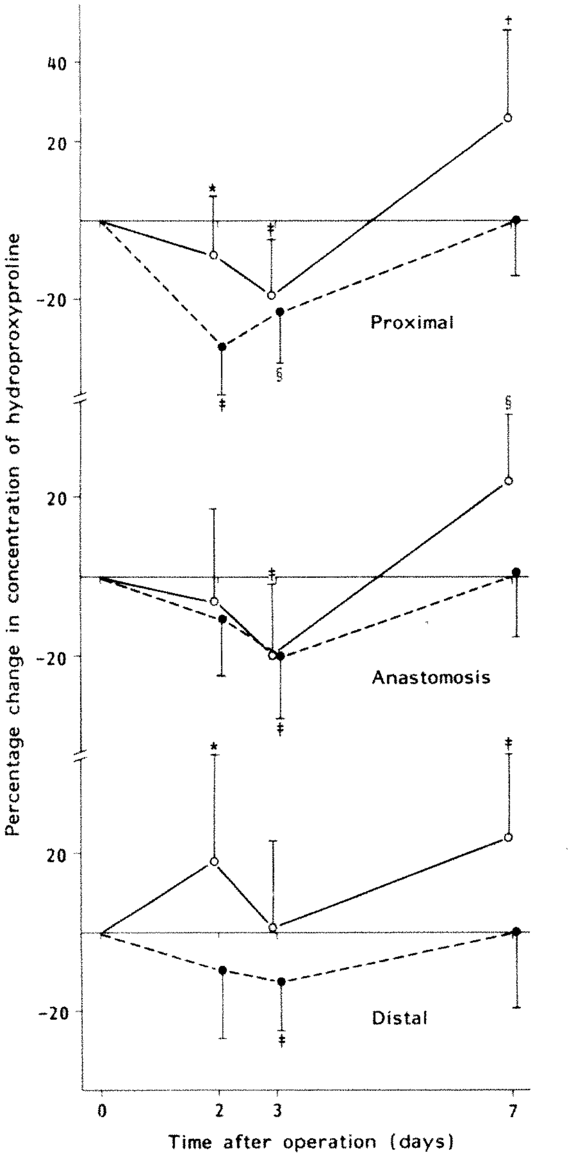

Figure 1 *Relative changes in hydroxyproline concentrations around ileal anastomoses. Results are expressed as mean percentage change, calculated with respect to the preoperative value, with standard deviation, for control (○) and germ-free (●) rats. Levels of significance for the difference between postoperative and control segments are calculated by means of a paired sample two-sided Student's* t *test and are represented as follows:* $*0{\cdot}05<P\leqslant0{\cdot}1$; $\dagger0{\cdot}01<P\leqslant0{\cdot}05$; $\ddagger0{\cdot}001<P\leqslant0{\cdot}01$; $\S P\leqslant0{\cdot}001$

pronounced in the colon; a significant difference was found between levels in uninjured colon and both the anastomosis proper and its proximal segment at all three time points. A similar phenomenon was seen in the ileum, where the effect was less marked and where preoperative levels were restored more rapidly. No lowering of hydroxyproline concentrations was seen in the area distal to the anastomosis. The transient reduction of hydroxyproline concentrations in proximal and anastomotic segments was also observed in germ-free rats. However, there were significant quantitative differences between the control and germ-free groups (*Table 2*). In the colon, the reduction of hydroxyproline levels was less marked in germ-free than in control rats, particularly in the anastomosis at 2 and 3 days and in the proximal segment at 3 days after operation. In the ileum, restoration of preoperative hydroxyproline concentrations appeared retarded in germ-free rats: at 7 days levels had only returned to preoperative values while at this time they were significantly enhanced in control rats.

As the changes in the immediate wound area are probably most relevant to the healing sequence, the apparent differences between germ-free and control rats in the anastomotic segment are of most interest. Hydroxyproline changes have been expressed in terms of concentrations (μg/mg dry weight). To determine whether the differences in postoperative hydroxy-

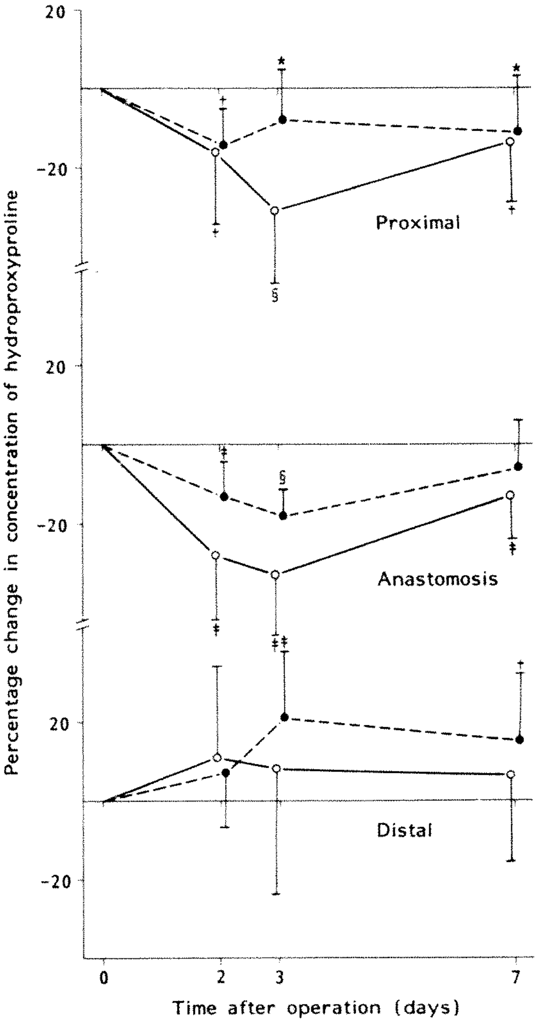

Figure 2 *Relative changes in hydroxyproline concentrations around colonic anastomoses. Results are expressed as mean percentage change, calculated with respect to the preoperative value, with standard deviation, for control (○) and germ-free (●) rats. Levels of significance for the difference between postoperative and control segments are calculated by means of a paired sample two-sided Student's* t *test and are represented as follows:* $*0{\cdot}05<P\leqslant0{\cdot}1$; $\dagger0{\cdot}01<P\leqslant0{\cdot}05$; $\ddagger0{\cdot}001<P\leqslant0{\cdot}01$; $\S P\leqslant0{\cdot}001$

Table 2 *Significant differences in postoperative hydroxyproline changes between control and germ-free rats*

	Day on which rats killed	Segment	Mean percentage change in hydroxyproline concentration		*P* value (control *versus* germ free)
			Control	Germ free	
Ileum	2	Proximal	−9	−32	0·0047
		Distal	18	−10	0·0295
	7	Proximal	26	0	0·0330
		Anastomosis	24	1	0·0142
		Distal	24	1	0·0387
Colon	2	Anastomosis	−28	−13	0·0423
	3	Proximal	−31	−8	0·0033
		Anastomosis	−33	−18	0·0063

Results are expressed as mean percentage change, calculated with respect to the preoperative value. Levels of significance for the differences between germ-free and control rats are calculated by means of a Wilcoxon two-sided unpaired test

Table 3 *Weight of ileal control and anastomotic segments*

	Day on which rats killed	*n*	Peroperative control segment	Postoperative anastomotic segment	Anastomotic segment/ control segment
Control rats	2	10	13·4 (2·9)	18·7 (3·6)	1·46 (0·38)
	3	10	12·0 (4·3)	28·5 (8·6)	2·73 (1·46)
	7	10	9·6 (2·9)	35·6 (7·0)	4·03 (1·52)
Germ-free rats	2	7	6·6 (2·5)	15·6 (2·4)	2·65 (0·87)
	3	11	6·5 (3·0)	17·5 (5·6)	3·03 (1·23)
	7	7	9·3 (1·6)	38·3 (7·1)	4·22 (0·98)
C_2 *versus* GF_2*			$P=0{\cdot}0012$	$P=0{\cdot}0185$	$P=0{\cdot}0038$
C_3 *versus* GF_3			$P=0{\cdot}0146$	$P=0{\cdot}0083$	n.s.
C_7 *versus* GF_7			n.s.	n.s.	n.s.

Results are expressed as mean weight (s.d.) in milligrams per centimetre of segment. Differences between germ-free and control rats are tested for significance by means of a Wilcoxon two-sided unpaired test. C, control; GF, germ-free; n.s., not significant; *subscript numbers refer to the day on which rats were killed

Table 4 *Weight of colonic control and anastomotic segments*

	Day on which rats killed	*n*	Peroperative control segment	Postoperative anastomotic segment	Anastomotic segment/ control segment
Control rats	2	10	10·2 (3·8)	22·3 (6·3)	2·22 (0·99)
	3	10	10·0 (3·0)	25·8 (6·9)	2·69 (0·70)
	7	10	7·9 (1·5)	20·4 (4·4)	2·69 (0·87)
Germ-free rats	2	7	8·0 (1·4)	18·9 (3·8)	2·42 (0·57)
	3	11	7·5 (2·5)	19·1 (5·1)	2·69 (0·78)
	7	7	8·1 (2·0)	22·7 (3·5)	2·88 (0·62)
C_2 *versus* GF_2*			n.s.	n.s.	n.s.
C_3 *versus* GF_3			$P=0{\cdot}0699$	$P=0{\cdot}0317$	n.s.
C_7 *versus* GF_7			n.s.	n.s.	n.s.

Results are expressed as mean weight (s.d.) in milligrams per centimetre of segment. Differences between germ-free and control rats are tested for significance by means of a Wilcoxon two-sided unpaired test. C, control; GF, germ-free; n.s., not significant; *subscript numbers refer to the day on which rats were killed

proline concentration changes may be attributed to differences in hydroxyproline content rather than to differences in dry weight (per centimetre of anastomotic segment), we have compared the changes in dry weight of the anastomotic segments for the ileum (*Table 3*) and the colon (*Table 4*). The weight of uninjured intestine was higher in control rats than in germ-free rats: 1 cm of ileum weighed 11·7 (3·7) mg in control rats (mean and s.d.; $n=30$) and 7·3 (2·7)mg ($n=25$) in germ-free rats ($P<0{\cdot}0001$); values for colon were 9·4 (3·0) and 7·8 (2·1)mg ($P=0{\cdot}02$), respectively. In the ileum, the weight of the anastomotic segment increased with time, while it remained constant in the colon. The increase in weight relative to that of the control segment was similar in control and germ-free rats, except in the ileum 2 days after operation. Likewise, there were no significant differences in the weight change of the proximal segment in germ-free and control rats (results not shown), except in the ileum after 2 days, where the weight gain was significant in germ-free rats.

Finally, total protein concentrations were measured in those segments where the reduction in hydroxyproline levels was most

Table 5 *Colonic protein concentrations in control and anastomotic segments 2 and 3 days after operation*

Days on which rats killed	*n*	Control segment	Anastomotic segment	Anastomotic segment/control segment
Day 2				
Control	9	695 (80)	686 (54)	0·99 (0·07)
Germ-free	7	719 (51)	666 (37)	0·93 (0·06)
Day 3				
Control	10	686 (45)	666 (41)	0·97 (0·07)
Germ-free	11	691 (78)	675 (36)	0·99 (0·11)

Results are expressed as mean value (s.d.) in micrograms per milligram

pronounced (i.e. in the colon anastomoses 2 and 3 days after operation). *Table 5* shows that there was no significant decrease in protein concentration in any of the groups investigated.

Discussion

The negative influence of micro-organisms on anastomotic healing in the large bowel has often been suggested[14–15]. Indeed, bowel preparation with antibiotics and irrigation appears to be beneficial to healing of experimental and human colonic anastomoses[16–20]. The mechanism whereby intraluminal bacteria affect wound healing remains a matter for speculation, but interference with anastomotic collagen metabolism could be involved. Therefore, it is of interest to investigate the behaviour of collagen concentrations in animals whose digestive tract is completely free from bacterial contamination. In the present study, operations on germ-free rats kept in a horizontal laminar flow workstation yielded a relatively high contamination rate (44 per cent) but provided enough uncontaminated rats for analysis.

The importance of collagen in maintaining and restoring the structural integrity of the intestinal wall seems undisputed. The concept that the 'collagenous equilibrium' is crucial for undisturbed healing is widely accepted[8]. Both collagen degradation and collagen synthesis are inherent in the healing sequence. Investigations into the healing process of intestinal anastomoses frequently comprise measurements of hydroxyproline concentration (per milligram dry weight) or hydroxyproline content (per centimetre). Neither allows quantitative conclusions regarding the separate processes of collagen degradation and synthesis, as a given level at a certain time only reflects the net result. However, the postoperative decrease in hydroxyproline concentration is taken to support the assumption that collagen degradation occurs. Comparison of the course of change in hydroxyproline concentrations during the first postoperative days in various groups of animals is meaningful if it can be shown that eventual differences are the result of changes in collagen content, rather than changes in total dry weight. Thus, if we want to compare changes in hydroxyproline concentrations around anastomoses in control and germ-free rats, it appears pertinent to show that the development of the increase in dry weight in the various segments is similar in both types of rat. This is shown in *Tables 3* and *4* for the anastomotic segment, where the events must have the most direct effect on wound strength. While the absolute weight of segments from uninjured intestine from germ-free rats was smaller than that from control rats, it can be seen that, with one exception in the ileum, the relative increase in anastomotic weight was identical in both types of rat. Therefore, differences in hydroxyproline concentrations may be attributed to differences in collagen metabolism. In control rats, the postoperative decrease in hydroxyproline concentration was most pronounced in the colonic anastomosis; total protein content did not change. In germ-free rats, reduction of hydroxyproline levels still occurred but was consistently and significantly less pronounced. The same difference between control and germ-free rats was found in the proximal segment, particularly after 3 days. These results are taken as evidence that in the colon bacteria contribute to the postoperative degradation of collagen in the anastomotic area. This seems not to be the case in the ileum. Here, the increase in hydroxyproline observed after 7 days in control rats was significantly reduced in germ-free rats. This could mean that bacteria also affect (in a negative way) collagen synthesis.

As a result of the absence of exposure to bacteria, germ-free rats differ in many respects from normal Wistar rats[21,22]. Their cardiac output is 30 per cent lower, the regional blood flow in many organs is reduced, and they do not possess a stimulated immune-response system. Differences are also found in the intestinal tract: the small intestine appears somewhat thin walled (cf. *Table 3*), the caecum is much larger and the large bowel content is more liquid than in conventional experimental rats. Despite these differences, it is our contention that our data support the hypothesis that colonic flora may be detrimental to colonic healing by affecting collagen metabolism. One result of construction of an anastomosis seems to be increased collagenolytic activity[23]. As bacteria contain collagenase activity they might directly enhance postoperative collagen breakdown[9]. Alternatively, their presence could strengthen the inflammatory response and thus the activity and enzyme production of granulocytes, which are also a rich source of collagenolytic activity[24]. Collagen synthesis by fibroblasts is also an integral part of the healing sequence. Bacteria could also interfere with anastomotic healing by parasitizing available oxygen from tissue fibroblasts and thus decreasing their synthesizing capabilities[25].

The present results allow no conclusions about which of these possibilities are correct, although the results observed in the ileum after 7 days argue against bacterial inhibition of collagen synthesis. They only support the idea that bacteria do indeed affect postoperative collagen levels in the intestinal wall. Further confirmation of their role should come from studies of the effect of bacteria on the separate processes of collagen degradation and synthesis.

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Case report

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Juvenile polyp in an ileoanal J pouch following restorative proctocolectomy for juvenile polyposis coli

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A juvenile polyp is described developing within ileal mucosa in an ileoanal J pouch 10 months after restorative proctocolectomy for severe juvenile polyposis coli. We believe that this is the first recorded case of a hamartomatous juvenile polyp arising in the mucosa of an ileal pouch.

Case report

A 16-year-old male patient was referred for definitive treatment of juvenile polyposis coli. He gave an 8-month history of intermittent rectal bleeding, prolapsing rectal polyps and profound anaemia (5 g/dl) requiring several blood transfusions. Colonoscopy revealed hundreds of polyps throughout the large bowel with prominent clusters in the rectum and caecum. His mother also had colonic polyps but these were fewer in number and almost entirely confined to the rectum. No other close relative was affected.

The patient underwent restorative proctocolectomy with formation of a J ileal pouch and ileoanal anastomosis. No polyps were seen in the 30 cm of ileum used to construct the pouch. Histopathological examination of the colon confirmed juvenile polyposis coli. The polyps were composed of oedematous chronically inflamed lamina propria covered by focally ulcerated colonic epithelium with no evidence of dysplasia or neoplasia. After closure of the covering ileostomy the pouch functioned satisfactorily 4–5 times per day with complete continence and no further bleeding.

Ten months later the patient again became anaemic, complaining of bleeding from the pouch and of a prolapsing lump obstructing defaecation until pushed aside by a finger. He required further blood transfusion. Examination under anaesthetic revealed a pedunculated polyp, 3 cm in diameter, arising from ileal mucosa and prolapsing through the anus. The stalk was transfixed and the polyp excised (*Figure 1*). Histology showed this to be another juvenile polyp covered predominantly by epithelium of small intestinal type although foci of gastric (pyloric) and colonic metaplasia were noted (*Figure 2*). There was no evidence of dysplasia or neoplasia. The patient made a satisfactory recovery but a later small bowel enema examination has demonstrated the presence of a number of polyps in the small bowel which are, as yet, asymptomatic.

Discussion

Multiple juvenile polyposis may be sporadic or inherited as an autosomal dominant. The polyps develop either in the large bowel alone or in the whole gastrointestinal tract. There is said to be a very small risk of malignancy in this condition compared with that associated with familial adenomatous polyposis[1].

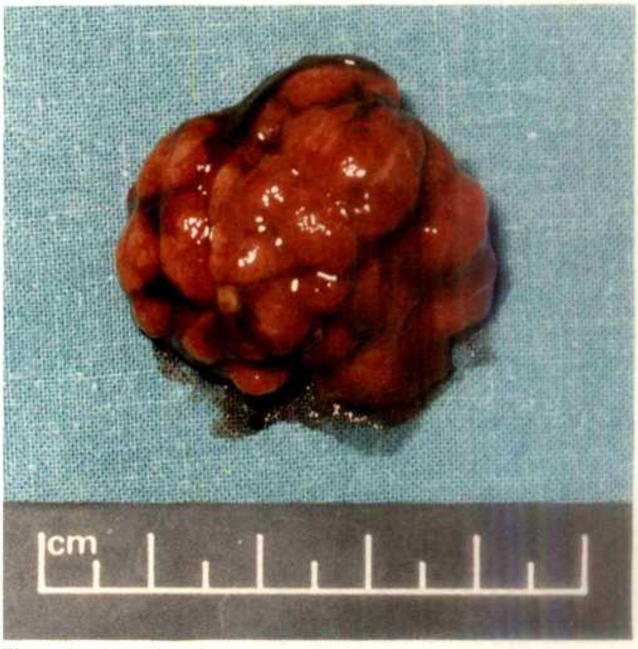

Figure 1 *Juvenile polyp recovered transanally from ileal pouch*

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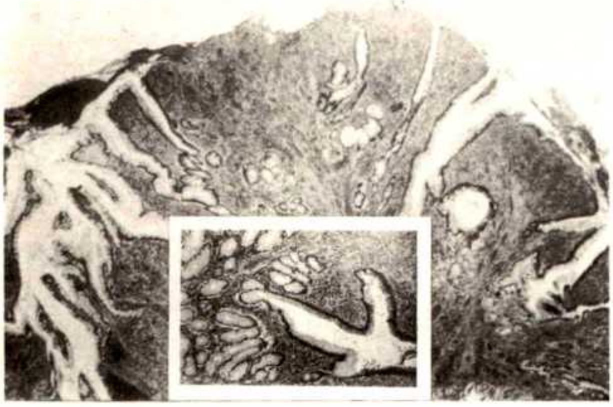

Figure 2 *Polyp from ileal pouch with prominent lamina propria showing surface ulceration. It is lined mainly by small intestinal epithelium but (inset) demonstrates foci of pyloric and colonic metaplasia. (Original magnification ×60)*

Adenomatous polyps have also been described in cases of juvenile polyposis[2,3]. If the rectum is relatively spared of polyps it is not generally necessary to perform proctocolectomy: subtotal colectomy with ileorectal anastomosis and local diathermy are usually sufficient. In the above case, however, there was severe rectal involvement, with bleeding, profound anaemia and prolapse. Serious complications of multiple juvenile polyposis necessitating urgent colectomy include intractable bleeding and severe fluid and electrolyte losses[4,5].

A juvenile polyp is a hamartomatous development of the lamina propria. In our case the polyp appeared to have developed from the pouch mucosa because its pedicle was about 5 cm long and no polyps were noted during the construction of the pouch. It is known that benign neoplasia of the small bowel occurs in patients with familial adenomatous polyposis and adenomatous lesions have been described in the Kock ileal reservoir after proctocolectomy for familial adenomatous polyposis[6,7]. The pouch polyp in our case was a juvenile polyp developing in previously normal-looking ileal mucosa lining the ileal pouch, and we believe this is the first such case on record.

This polyp showed some of the inflammatory features described in the ileal pouches of patients with ulcerative colitis and familial adenomatous polyposis; this includes colonic metaplasia, which has been suggested may predispose to later neoplasia[8]. Regular surveillance has been recommended for pouches fashioned in cases of familial adenomatous polyposis[9]. In view of our findings we would extend this recommendation to include regular surveillance of all cases with ileal reservoirs performed for polyposis whether adenomatous or otherwise.

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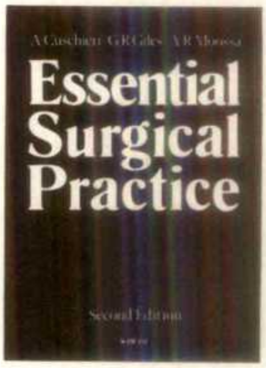

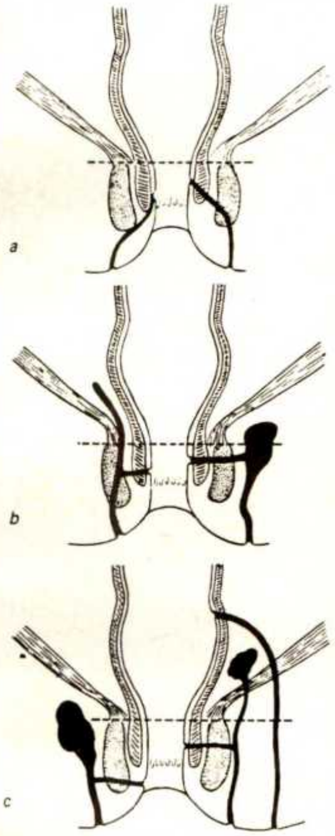

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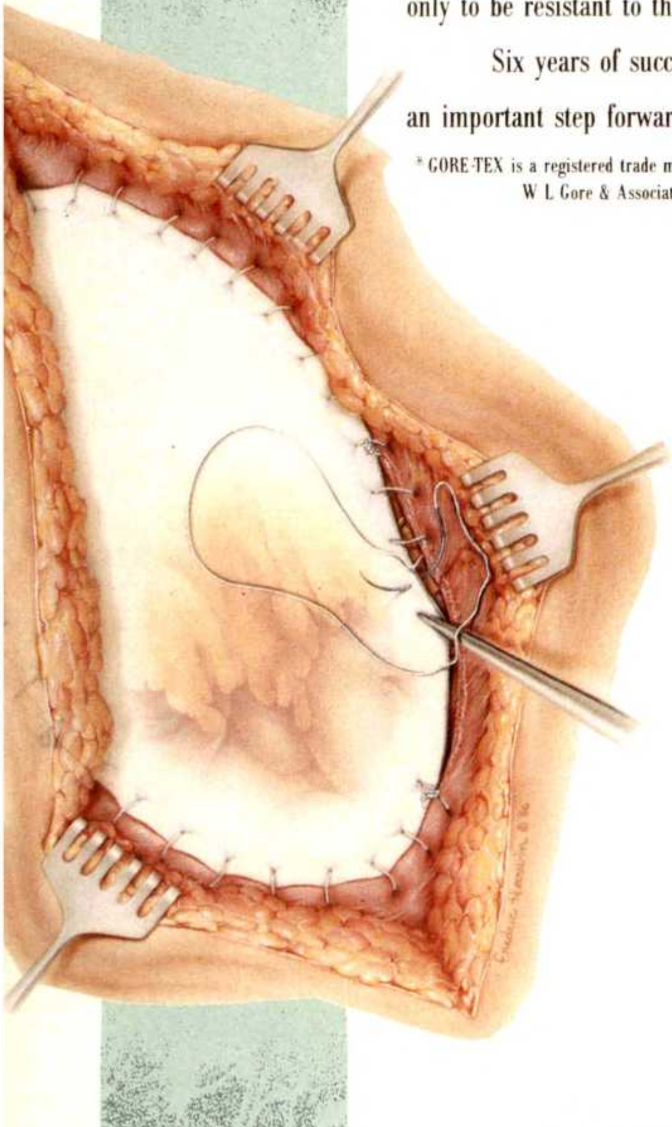

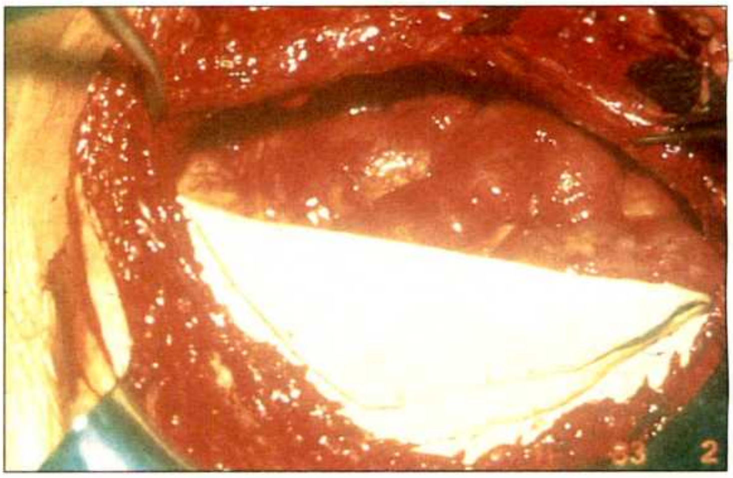

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Expanded polytetrafluoroethylene (ePTFE) was used to repair 11 large abdominal wall defects in ten patients. Three patches were fixed to the adjacent abdominal aponeurosis with a single row of sutures; seven patches were implanted with a 1–2 cm overlap of patch and aponeurosis and a double row of sutures. Recurrent buttonhole hernias were found in two patients, in both of whom a single row of sutures had been used. This reherniation was due to insufficient anchorage of the patch to the fascia. It is concluded that ePTFE is a useful material to repair large abdominal wall defects provided the patch is fixed to the aponeurosis with an overlap and a double row of sutures to prevent buttonhole hernias.

Keywords: Hernia (ventral), expanded polytetrafluoroethylene, soft tissue patch

Large abdominal wall defects resulting from trauma, necrotizing infection, tumour resection or other causes continue to be a major problem for both patients and surgeons. The lack of sufficient tissue may require the insertion of a prosthetic material. Polypropylene mesh (Marlex®, C.R. Bard Incorporated, Murray Hill, New York, USA) is still the most widely used material for this purpose. It is relatively cheap and usually suffices well, although its propensity for inducing extensive visceral adhesions and occasional fistulation is a well recognized drawback[1–5].

Recently, an expanded polytetrafluoroethylene (ePTFE) patch (GORE-TEX® Soft Tissue Patch, W.L. Gore and Associates Incorporated, Flagstaff, Arizona, USA) has been introduced. Thus far, only two reports have been published in the English literature on the clinical use of this material for the reconstruction of large abdominal wall defects, involving in all 29 patients[6,7].

The present report extends this experience with the long-term results obtained in ten patients treated in our department, illustrating two important problems that can be encountered by using this material: buttonhole hernia and erythema of the skin in combination with prolonged subfebrile temperature.

Patients and methods

Between April 1985 and August 1986, 11 abdominal wall defects in ten patients were reconstructed with ePTFE. There were four men and six women with a mean age of 47 years (range 9–72 years). In all instances, the defect was too large for primary closure and omentum was not available for interposition between viscera and patch. Four defects were associated with recurrent incisional hernia, three with open treatment of generalized peritonitis and one with tumour resection. Two defects were congenital in origin. The dimensions of the hernias varied between 5 × 10 cm and 15 × 20 cm. Two patients, who had previously been treated with Marlex mesh after open treatment of generalized peritonitis, showed persistent fistulation. The remaining operations were performed in a clean uncontaminated field.

Standard sterile surgical procedures were performed. No antibiotic prophylaxis was used. The skin was disinfected with iodine tincture. The fascial margins of the hernia were identified and, if necessary, the peritoneal cavity was explored to dissect any loops of intestine adherent to the parietal peritoneum near the fascial margin. An ePTFE patch of 2-mm thickness was tailored to the desired shape so as to cover the fascial gap without excessive tension. The patch was sutured with interrupted polypropylene 0 sutures to the fascial margin with no overlap between fascia and patch in three patients, and with a 1–2 cm overlap and a double row of sutures in all the other patients (*Figure 1*).

Postoperatively, the wounds were inspected daily during hospital stay, at intervals of 3–4 months during the first year, and at yearly intervals thereafter. No patients were lost to follow-up.

Results

The mean follow-up was 31·5 months (range 21–41 months). Early postoperative complications were subcutaneous haematoma ($n = 1$), seroma ($n = 1$), and erythema of the overlying skin combined with subfebrile temperature during the first postoperative week ($n = 2$). These complications were transient and required no surgical intervention.

Primary wound healing with an uneventful postoperative course was observed in seven patients. Postsurgical complications requiring reintervention were observed in three patients.

One of two patients with persistent fistulation after previous Marlex implantation developed a postoperative wound infection. Systemic antibiotic treatment was unsuccessful, and when the ePTFE patch was removed 1 month after operation it had completely deteriorated. It was surrounded by large amounts of purulent exudate, but a thick layer of fibrous tissue was observed under the patch. The remaining wound defect was partly closed without prosthetic material and healed well. No hernia recurred, probably because of the fibrous tissue that

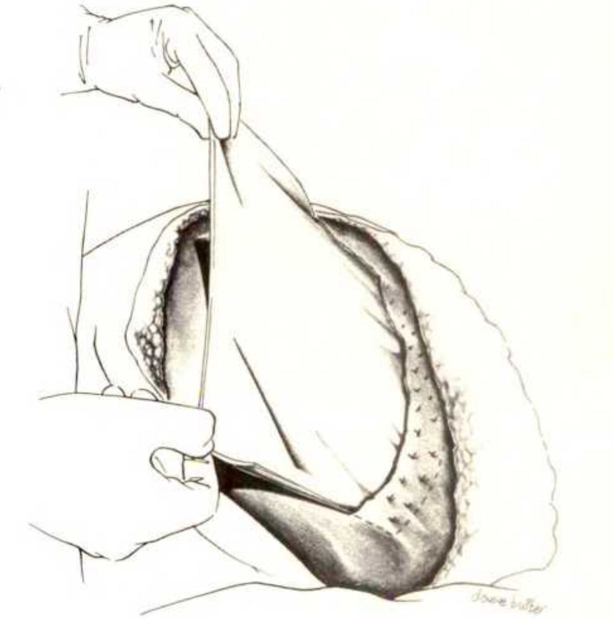

Figure 1 *An ePTFE patch implanted tension-free as a full-thickness implant in a large abdominal wall defect. The patch is fixed to the fascia with a double row of sutures and an overlap of 1–2 cm*

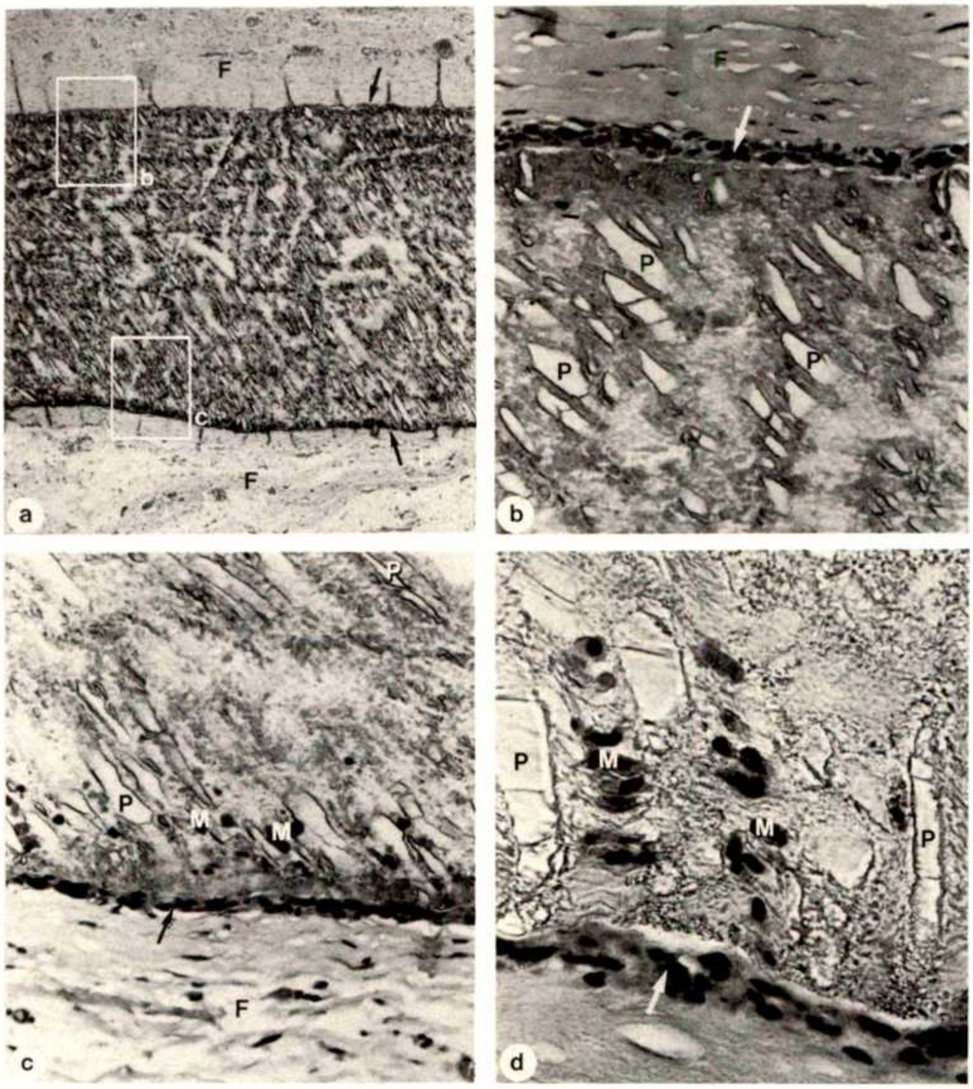

Figure 2 *Light micrographs of an expanded polytetrafluoroethylene (ePTFE) patch that was explanted 6 months after implantation because of recurrence of four buttonhole hernias at the patch–fascia inferface.* **a** *Overview of the patch with* **b** *detail of the skin-side and* **c** *and* **d** *details of the peritoneal side. Note that the patch is entirely surrounded by a zone of macrophages (arrows) that form a barrier between patch and surrounded fibrocollagenous tissue (F). At the peritoneal side* (**c** *and* **d**) *some macrophages (M) could be found in the outermost internodal spaces. P, PTFE node. (Stained with haematoxylin and eosin; original magnifications:* **a**, *× 30;* **b** *and* **c**, *× 200;* **d**, *× 500)*

had formed underneath the ePTFE patch. Cultures revealed *Staphylococcus aureus*.

Reherniation was observed in two of the three patients in whom the patch had been inserted with a single row of sutures and without overlapping the fascial margin. In both patients bowel appeared to herniate between sutures at the patch–fascia interface (i.e. buttonhole hernias). In one patient, a single buttonhole hernia of about 1 × 2cm between the patch and the fascial margin was observed 2·5 months after operation. This defect was successfully treated by placing two additional stitches between the patch and the fascia. In the other patient, four small buttonhole hernias, each of about 1 × 2 cm, were observed between the patch and the fascia 3 months after operation. In this case the patch was removed 6 months after the initial operation. There appeared to be minimal loose adhesions between the bowel and the patch. A new, larger ePTFE patch (10 × 20 cm) was implanted by means of the double row of sutures with overlap technique, and the subsequent course was uncomplicated. Histological analysis of serial sections of the removed patch showed absence of ingrowth of fibrocollagenous tissue into the patch (*Figure 2*). A similar histological pattern was seen in a second patient in whom a patch was removed during the construction of a continent urostoma, 41 months after implantation.

A good result was ultimately achieved in all instances. All patients took up their normal activities and regained a normal abdominal wall contour with no puckering and no rigidity to betray the underlying patch.

Discussion

Our report illustrates the clinical efficacy of ePTFE for the reconstruction of large abdominal wall defects. It also draws attention to two pertinent aspects that have not previously been reported: the erythema of overlying skin and the subfebrile temperature which may transiently occur soon after operation; and the importance of using the double row of sutures with overlap technique (*Figure 1*) to prevent recurrence of buttonhole hernias.

Recent experimental[8,9] and clinical[6,7] data strongly suggest that ePTFE closely meets the ideal prosthetic material to repair abdominal wall defects. Our present study corroborates these findings as we, like Bauer *et al.*[7], observed no gross interference of the ePTFE patches with wound healing, no fistulation and no intestinal obstruction. Moreover, at explantation of two patches we found only minimal loose adhesions to the bowel and a low-grade inflammatory reaction around the patches.

Unlike others, however, we observed a rather conspicuous reaction after implantation of an ePTFE patch; this occurred in two patients, who showed erythema and prolonged subfebrile temperature in the postoperative period. The clinical importance of this phenomenon lies in the fact that it should not be confused with signs of infection.

The present study seems to advocate the use of the double row of sutures with overlap technique (*Figure 1*) for the implantation of ePTFE patch to prevent recurrence of hernias. Although our series of patients is small, we observed recurrence of hernias only in those patients in whom no double row of sutures and overlap had been used (two of the three patients). Recurrence of these hernias (all occurred within the first few months) was observed at re-exploration to be due to herniation of bowel between sutures at the patch–fascia interface (i e. buttonhole hernias). Moreover, histological analysis of two patches at 6 and 41 months after the original operation revealed poor anchorage of fibrocollagenous tissue to the patch: the fibrocollagenous tissue was separated from the patch by a zone of macrophages (*Figure 2*). Also, the internodal space of the ePTFE patches (fibril length 10–20 μm) is too small to allow good ingrowth of fibrocollagenous tissue. Even PTFE material with a fibril length of 30 μm permits little tissue ingrowth[10]. This actually indicates that anchorage at the patch–fascia interface depends mainly on the suture technique at the patch–fascia interface. This idea is supported by an observation of Bauer *et al.*[7] who at exploration of a buttonhole hernia in a patient found a single polypropylene suture untied and free at the ePTFE patch–fascia interface. It seems that the double row of sutures with overlap technique (*Figure 1*) is a method that eliminates the risk of reherniation of bowel at the patch–fascia interface.

Infection occurred in one patient (one of the two patients who had a contaminated operation field). Although ePTFE is less adherent for bacteria compared with polypropylene mesh[11], its use in contaminated wound areas should be avoided. Recent experimental studies in our laboratory revealed that ePTFE, when used to reconstruct contaminated abdominal wall defects, showed a significantly higher incidence of infection and patch extrusion compared with polypropylene mesh[12]. Additional coating of an ePTFE patch with antibiotics may improve its resistance to infections, as has already been demonstrated for ePTFE arterial prostheses[13], and may broaden the indication for its clinical use.

In conclusion, the present study underlines the clinical usefulness of ePTFE material for the reconstruction of large abdominal wall defects. Because of the costs of this material, and the result with Marlex, we reserve this material for patients in whom the underlying peritoneum cannot be re-established and in whom there is insufficient omentum. The patch should be implanted with a 1–2 cm overlap between fascia and patch and a double row of sutures to prevent recurrence of buttonhole hernias. Erythema and prolonged subfebrile temperature may be observed in some patients. More clinical data should determine the ultimate place and indication for the ePTFE patch.

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Squamous cell carcinoma of the anus at one hospital from 1948 to 1984

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Two hundred and twenty-eight patients with anal carcinoma treated between 1948 and 1984 were reviewed. Of 145 with anal canal carcinoma, 118 were treated by total anorectal excision, nine by local excision and 13 by radiotherapy. Fifteen patients were inoperable. There were five postoperative deaths. Crude and cancer-specific survival rates of 123 patients treated 5 or more years previously were 58 and 64 per cent. These rates for patients undergoing total anorectal excision were 62 and 65 per cent, and local excision 87 and 100 per cent. Eighty-three patients had carcinoma of the anal margin. Of these, 55 were treated by local excision, 18 by total anorectal excision and 20 by radiotherapy. Eight patients were inoperable. Crude and cancer-specific survival rates for 72 patients followed for 5 years were 55 and 57 per cent with respective rates of 65 and 69 per cent after local excision and 36 and 40 per cent after total anorectal excision. The 5-year survival rate of 27 patients with TNM N_1 stage was 48 per cent. Histological confirmation was obtained in only nine of these patients, however, but five (55 per cent) survived 5 years after block dissection or radiotherapy. Metachronous lymphadenopathy occurred in 25 patients. The 5-year survival rate in the 23 cases that were histologically confirmed was 35 per cent after block dissection (17 cases) and radiotherapy (four cases). Using a modification of Papillon's T classification for anal canal carcinoma, stage correlated with survival after combining T_1 with T_2 tumours and T_2 with T_3 tumours. Five-year survival rates in these groups were 60 and 54 per cent respectively. The TNM–UICC classification for anal margin carcinoma correlated with survival in a similar manner. The 5-year survival rate was 65 per cent for patients with T_1 and T_2 tumours and 33 per cent for those with T_3 and T_4 tumours.

Keywords: Anal cancer, surgical treatment, staging

There has been renewed interest in squamous cell carcinoma of the anus owing to the increasing use of radiotherapy and chemotherapy as treatment[1–13]. Although the incidence of the disease in England and Wales has been stable over the last 10 years, it is quite possible that there will be an increase in the future, given the rise in prevalence of human papilloma virus-related disease[14]. Anal cancer is, however, uncommon and few large series have been reported[5,12,13,15–18]. Some may not be comparable owing to confusion in the definition of anal margin and anal canal carcinoma and also to the inclusion of other types of anal cancer. Comparison of one study with another is also made difficult by differences in local staging systems which include those defined by the UICC (International Union against Cancer), Papillon and the Mayo Clinic[17] (*Table 1*). The last of these does not appear to have been adopted widely. The UICC classification is probably the most frequently applied but there has been no published attempt to validate it by comparing T stage with the clinical outcome.

With these considerations in mind, we set out to review the results of treatment of squamous cell carcinoma of the anus at one hospital. As a predominantly surgical series involving few surgeons, relatively large numbers of patients and a high rate of follow-up, it should provide useful up-to-date information on the results of surgery with which other treatments might be compared.

The last report from this hospital in 1968[19] included all cases treated from 1928 up to that time. In the present study, however, it was decided only to include patients who had been treated since 1948. By then the operability rate had risen to a stable figure of about 90 per cent. Thus the patients included were managed by a similar strategy based on the optimal use of surgery, with radiotherapy being used in a minority.

We also attempted to relate local features of the tumour, determined by clinical examination, to survival. Sufficient clinical information was available to enable the classification of Papillon to be applied to tumours of the anal canal and the TNM–UICC classification to those of the anal margin (*Table 1*).

Table 1 *Carcinoma of the anus: definition of T stage*

T stage	Anal canal (Papillon, 1982) modified	Anal margin (TNM—UICC, 1978)
T_1	<2 cm	T_1 <2 cm
T_2	2 cm to ≤5 cm	T_2 2 cm to ≤5 cm
T_3	>5 cm	T_3 >5 cm
T_{4a}	Invading vaginal mucosa	T_4 Extension to muscle, bone etc.
T_{4b}	Invading neighbouring structures other than skin, rectum or vagina	
T_x	Insufficient information available	

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Patients and methods

Between 1948 and 1984, 238 patients with squamous cell carcinoma of the anus were seen at the hospital. The case notes of all were studied and ten (4 per cent) were excluded, six because of the presence of synchronous or metachronous colorectal cancer, two in which the squamous cell carcinoma appeared to have arisen in the rectum and two with coincident Crohn's disease. Squamous cell carcinoma of the anus was defined according to the International Histological Classification of Tumours[18] and cases were divided into those occurring in the anal canal or at the anal margin on the criteria of Morson[20]. Anal canal tumours included those lying entirely above, mainly above or astride the dentate line. Tumours lying mainly below or entirely below this level were regarded to be arising at the anal margin.

Clinical staging

Local features of the tumour as recorded at the initial clinical examination were extracted from the case notes wherever this information was available. They included details of the longitudinal diameter, quadrant(s) involved, relationship to the dentate line and degree of local penetration (whether invading the internal sphincter, external sphincter or penetrating the external sphincter to invade other structures).

Anal canal carcinoma was classified using the staging system of Papillon modified to define stage T_2 as tumours from 2 to $\leqslant 5$ cm in diameter (not 2–4 cm as proposed by Papillon) and T_3 as tumours >5 cm in diameter. Anal margin carcinoma was classified using the TNM–UICC system without any modification[21,22] (*Table 1*).

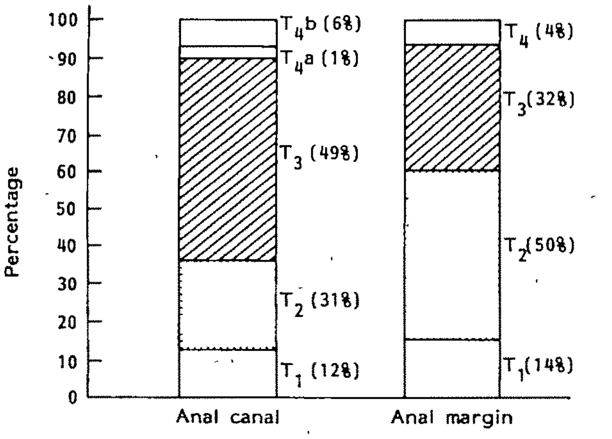


Figure 1 *Relative proportion of T stage at presentation of carcinoma of the anal canal and anal margin*

Table 2 *Anal canal carcinoma: type of treatment in 145 patients*

	No. of patients (%)	Radiotherapy (%)
Diagnosis only	3 (2)	0
Inoperable	15 (10)	13
Total anorectal excision	118 (81)*	9
Local excision	9 (6)	0
Total	145	22 (15)

* Includes five postoperative deaths

Sufficient information from the clinical notes was available to enable a T stage value to be given to 203 (89 per cent) of 228 cases, including 134 (92 per cent) of 145 patients with anal canal carcinoma and 69 (83 per cent) of 83 with anal margin carcinoma. Five-year survival rates were determined for each T stage in both the anal margin and anal canal carcinoma groups. Crude 5-year survival and cancer-specific 5-year survival rates were calculated. Survival rates were compared using the log rank test.

For the analysis of inguinal lymph node status, patients with anal canal and anal margin carcinoma were combined. The occurrence of synchronous or metachronous nodal involvement was determined from the notes. Details regarding histological confirmation, treatment and survival were recorded.

Results

There were 145 cases of anal canal and 83 cases of anal margin carcinoma.

Anal canal carcinoma

Of 145 patients, 65 were men and 80 women (male:female ratio 1:1·2). The median age at presentation was 58·7 years (range 28–87 years). The mean duration of symptoms was 10 6 months; patients with the disease most commonly presented with bleeding, pain or a lump in the anus. The distribution of T stage at presentation is shown in *Figure 1*. About half the cases were classified as stage T_3. Disseminated disease (M_1) was demonstrated at presentation in nine patients. Of 15 (10 per cent) patients considered inoperable, 13 were treated by radiotherapy (*Table 2*). The majority, 118 (81 per cent), underwent a total anorectal excision and only nine (6 per cent) were treated by local excision. Five (4 per cent) patients died in the postoperative period after total anorectal excision.

Eight (6 per cent) patients were treated less than 5 years before this study, five of the remaining 137 patients died postoperatively and five were not treated, leaving 127 patients eligible for 5-year assessment. Four of these were lost to follow-up; thus 123 patients were available for assessment of outcome at 5 years. The crude 5-year survival rate was 58 per cent (*Table 3*). Of the eight cases treated by local excision, crude and cancer-specific 5-year survival rates were 87 per cent and 100 per cent respectively. Three of the 13 patients considered inoperable who were treated by radiotherapy survived 5 years. Crude and cancer-specific 5-year survival rates after anorectal excision alone were 62 per cent and 65 per cent respectively for all cases and 71 per cent and 76 per cent for those without dissemination at the time of surgery.

Cumulative survival rates after treatment of anal canal carcinoma according to T stage are shown in *Figure 2*. There is a clear separation between T_1 and T_4 but a considerable overlap of T_2 and T_3 stages. The 5-year survival rates for patients with T_1 and T_2 tumours combined *versus* T_3 and T_4 combined of 60 per cent and 54 per cent respectively significantly different ($P>0{\cdot}05$).

Table 3 *Anal canal carcinoma: 5-year survival excluding operative deaths in 123 patients*

	All cases	Alive at 5 years	Cancer-specific survival	Curative cases	Alive at 5 years	Cancer-specific survival
Total anorectal excision	94	58 (62)	(65)	76	54 (71)	(76)
Local excision	8	7 (87)	(100)	7	6 (86)	(100)
Radiotherapy	13	3 (23)	(30)			
Total anorectal excision + radiotherapy	8	4 (50)	(67)			
Total	123	72 (58)	(64)			

Values in parentheses are percentages

Anal margin carcinoma

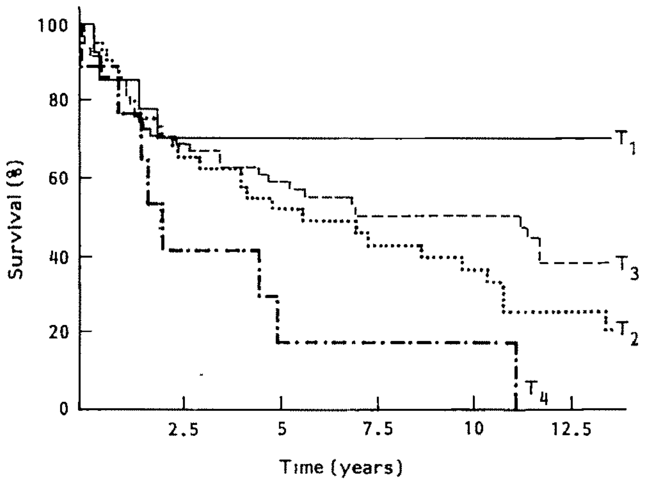
Of 83 patients, 57 were men and 26 women (male:female ratio 2·2:1). The mean age at presentation was 60·7 years (range 25–89 years): the average length of history was 9·2 months (range 0–65 months) and the nature and frequency of symptoms were similar to those of anal canal carcinoma. It was possible to assign a T stage to 69 (84 per cent) of 83 cases (*Figure 1*). The majority of lesions were early (T_1 and T_2, 64 per cent) and the incidence of more advanced lesions was less than that found in the anal canal (T_3 and T_4 in the anal margin, 36 per cent; T_3 and T_4 in the anal canal, 56 per cent). Four patients had demonstrably disseminated disease at presentation (M_1).

Two were seen for diagnosis only and one of the inoperable cases did not receive any radiotherapy (*Table 4*). The majority of the remainder underwent local excision (55 cases, 66 per cent). Radiotherapy was used in seven inoperable patients, in eight patients treated by local excision and in five of the 18 cases undergoing total anorectal excision. There were no postoperative deaths.

Crude and cancer-specific 5-year survival rates after excluding the two cases seen for diagnosis, the one inoperable case not treated and eight patients lost to follow-up are shown in *Table 5*. The results were very similar to those seen for anal canal carcinoma. Only one out of seven inoperable patients survived for more than 5 years after radiotherapy. Cumulative survival after treatment of growths according to T stage is shown in *Figure 3*. A similar pattern to that found in anal canal carcinoma was seen with survival of T_1 and T_2 combined (65 per cent), being significantly greater than that of T_3 and T_4 combined (33 per cent; $P<0·01$). There was no difference in the cumulative crude survival of anal canal and anal margin carcinoma (*Figure 4*).

Inguinal lymph node involvement

Twenty-seven (11 per cent) of the 228 patients were considered to have clinically involved inguinal nodes at presentation; biopsy was performed in 18 (67 per cent) cases and in only nine was tumour proved. Crude 5-year survival in the clinical N_1 group was 48 per cent and five (55 per cent) of the nine histologically confirmed cases were alive (*Table 6*). A further 25 (12 per cent) patients developed metachronous inguinal nodal enlargement; all were biopsied, and in 23 cases recurrence was confirmed. Nine (36 per cent) of these patients survived 5 years; block dissection was the commonest salvage treatment (17 cases), yielding a 41 per cent 5-year survival rate.

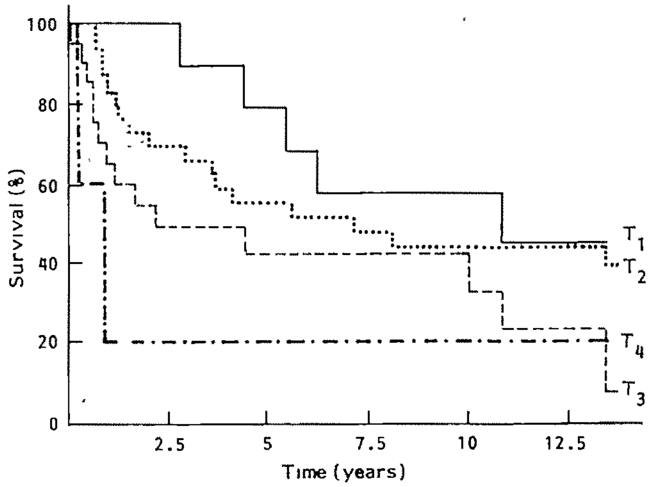


T_1	14	10	10	10	6	5
T_2	41	29	23	17	14	11
T_3	60	40	35	30	25	20
T_4	8	4	2	1	1	0

Figure 2 *Anal canal carcinoma: cumulative crude 5-year survival according to T stage (123 patients). The numbers of patients at risk are shown*

Table 4 *Anal margin carcinoma type of treatment in 83 patients*

	No. of patients (%)	Radiotherapy
Diagnosis only	2 (2)	0
Inoperable	8 (10)	7
Total anorectal excision	18 (22)	5
Local excision	55 (66)	8
Total	83	20



T_1	10	10	8	6	6	4
T_2	30	21	18	12	12	9
T_3	21	9	7	7	5	1
T_4	3	1	1	1	1	1

Figure 3 *Anal margin carcinoma cumulative crude 5-year survival according to T stage (64 patients) The numbers of patients at risk are shown*

Table 5 *Anal margin carcinoma 5-year survival in 72 patients*

	All cases	Alive at 5 years	Cancer-specific survival	Curative cases	Alive at 5 years	Cancer-specific survival
Total anorectal excision	11	4 (36)	(40)	11	4 (36)	(40)
Local excision	41	27 (65)	(69)	34	23 (68)	(72)
Radiotherapy alone	7	1 (14)	(20)			
Total anorectal excision + radiotherapy	5	2 (40)	(40)			
Local excision + radiotherapy	8	5 (62)	(62)			
Total	72	39 (55)	(57)			

Values in parentheses are percentages

Discussion

The present study is one of three large surgical series[12,13,23]. Anal margin and canal lesions have been separated by Morson's criterion of the relationship to the dentate line[20]. (Others draw the dividing line at the anal verge[17]). The 93 per cent follow-up rate at 5 years is high and information on treatment and histopathology have been well documented. The series encompassed the period from 1948 to 1984 when surgery was the treatment of choice and during which resectability had achieved a maximal figure. Treatment-related mortality was confined to five (4 per cent) cases among the 136 patients undergoing major surgery. Five-year survival in those with anal canal carcinoma appeared better than for anal margin lesions with respective rates for all cases of 58 per cent and 55 per cent and cancer-specific survival rates of 64 per cent and 57 per cent. There was a significant difference in survival of combined T_1 and T_2 lesions compared with T_3 and T_4 combined. Local recurrence figures are unfortunately not available for all patients but survival to 5 years is likely to imply absence of local recurrence.

The other large surgical series have obtained similar results. For example, at Memorial Hospital, New York, USA, a 5-year survival rate of 55 per cent after total anorectal excision for anal canal carcinoma was reported. Survival depended on the size of tumour, whether <2 cm (75 per cent) or >2 cm (40 per cent) in diameter. Of the 144 cases in the series only 11 (8 per cent) were treated by local excision and of these five survived 5 years[13,23]. Similarly in the present series only eight (6 per cent) of 145 cases of anal canal carcinoma underwent local excision but seven were alive 5 years later.

In a series of 128 patients with anal canal growths external irradiation using telecobalt produced survival rates of 68 per cent for those with stage T_2 or less and 32 per cent for those with stage T_3 or over[24]. Eschwege *et al.* reported very similar respective survival rates in 106 cases of 62 and 26 per cent with 42 per cent overall survival[25]. In both these series doses of 45–65 Gy were used according to a standard protocol. Many other radiotherapeutic series have not had either such large numbers or such a defined protocol For example, the treatment given to 51 patients at Princess Margaret Hospital, Toronto, Canada included various combinations of external beam and interstitial radiotherapy, although most received 45–50 Gy over 4–5 weeks[8]. The overall survival rate was 59 per cent at 5 years with local control achieved in 29 of 51 (57 per cent) patients. This survival rate, which is somewhat higher than in the series above, may be due to differences in the distribution of local stage within the groups but it is no greater than survival rates after surgery alone as reported by Greenall *et al.*[23] or in the present study.

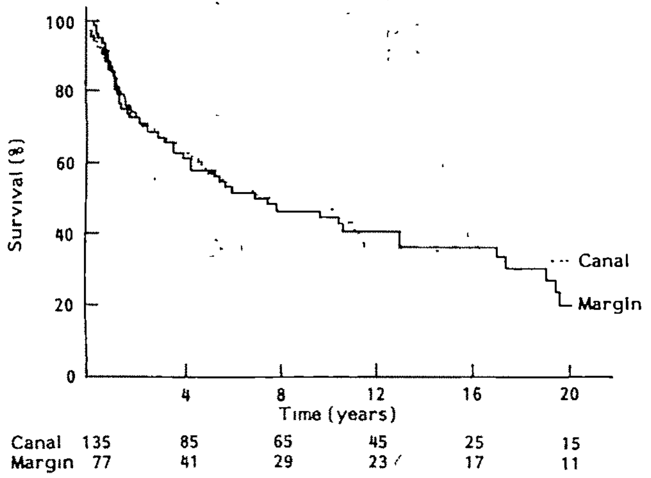


Figure 4 *Cumulative crude 5-year survival of all treated cases of anal canal and anal margin carcinoma (212 patients). The numbers of patients at risk are shown*

Interstitial radiotherapy used in 74 patients with carcinoma of the anal canal and anal margin produced cancer-specific survival at 5 years in 35 cases (51 per cent of 68 evaluable patients) There was, however, a need for salvage surgery in six patients for radionecrosis and 26 for recurrence. Survival was related to the initial size of the tumour (64 per cent, tumour <5 cm: 23 per cent, tumour >5 cm)[26].

Papillon has maintained that results of external beam radiotherapy can be improved by a split course of treatment[5,27]. This includes an initial irradiation by external beam to a dose of 30 Gy followed after an interval of 1·8 weeks by an interstitial implant of iridium for 24 h, adding a further 10–15 Gy. In a series of 158 patients with anal canal carcinoma followed for 5 years, only 20 per cent died of cancer and the overall crude disease-free survival rate was 65 per cent[5]. He pointed out that not all patients having radiotherapy avoided a colostomy but reported that 67 per cent of those with a T_3 stage tumour or less and 52 per cent with a T_4 stage tumour were alive and without a stoma at 5 years. These results certainly compare very well with those after major surgery and against other radiotherapy regimens. However, when comparing the overall results of surgery and radiotherapy, there is every indication that the former is as effective or more so than the latter in terms of survival and, as would be expected, the efficacy of each is related to local stage.

There has not been a satisfactory trial of combined radiotherapy and surgery for anal carcinoma This is due to the rarity of the disease, which has discouraged establishment of treatment protocols, and the introduction of multidisciplinary combined treatment developed by Nigro *et al.*[1,34]. In 31 patients initially treated by radiotherapy (30 Gy) and chemotherapy (5-fluorouracil and mitomycin C) followed by anorectal excision, no tumour was found in the operative specimen in 22 (71 per cent). As a result patients have subsequently been submitted to examination under anaesthesia with biopsy of the tumour site only after the initial treatment. In only one of 61 patients so treated was the biopsy positive and only seven cases have developed a late recurrence (treated by total anorectal excision). Of 20 deaths occurring in 104 patients, 13 have been due to recurrence[4]. These encouraging results

Table 6 *Clinical inguinal lymph node involvement in 228 patients*

		Histological status			Treatment (pathology positive)		
	No of patients	No histology obtained	Histology negative	Histology positive	Block dissection	Biopsy only	Radiotherapy
Synchronous							
Total no of patients	27	9	9	9	4	1	4
Alive at 5 years	13 (48)	4 (44)	4 (44)	5 (55)	3	—	2
Metachronous							
Total no. of patients	25	0	2	23	17	2	4
Alive at 5 years	9 (36)	—	1	8 (35)	7	1	1

Values in parentheses are percentages

have led others to adopt this treatment but the 5-year survival rates of adequate numbers of cases prospectively staged before treatment are not yet known. Randomized controlled trials of this treatment regimen are required and the results of the present surgical study should be useful for comparison because they represent the application of surgery to its maximal capacity.

Clinical staging

The TNM–UICC classification[22] applied to anal canal carcinoma includes four stages (T_{1-4}) based on the degree of penetration of the sphincter muscles and structures beyond. Such assessment is clearly a difficult exercise for the clinician and there are no data supporting its validity. Indeed the only study available has shown no relationship between survival and UICC T stage[8]. Most other clinical staging systems for anal canal carcinoma have not been generally accepted[17,28,29] but the simplicity of Papillon's classification based mainly on the diameter of the tumour should be readily applicable. In his own series of 66 patients followed for 5 years, Papillon reported survival rates of 76 per cent for T_1 and T_2 tumours and 61 per cent for T_3 tumours with local failure rates of 10·2 per cent and 24 per cent respectively. We have also been able to show a similar relationship between a slightly modified Papillon T stage in survival in the present study, discrimination being greatest between T_1 and T_4 tumours and for T_1 and T_2 combined, on the one hand, and T_3 and T_4 combined, on the other. The TNM–UICC system applied to anal margin carcinoma in the present series was also related to survival but again only when stages T_1 and T_2 and stages T_3 and T_4 were combined. Thus a separation of tumours into those >5 cm and those $\leqslant 5$ cm in diameter appears to be a useful indicator of prognosis and is also simple to apply. In neither anal canal nor anal margin carcinoma was there any significant survival difference between T_2 and T_3 lesions.

From the results of this study and that of Papillon, it seems justified to suggest that anal canal and anal margin carcinoma can each be divided into two clinical groups, i.e. tumours >5 cm or $\leqslant 5$ cm in diameter.

Inguinal lymph nodes

Clinical inguinal lymph node involvement was found to correspond with the presence of metastatic tumour in only half the cases biopsied. This suggests that enlarged nodes may often be due to chronic infection in the primary tumour. Previous reports have drawn attention to the difference in survival rates of patients with synchronous and metachronous metastases. For example, Greenall *et al.*[13] reported 5-year survival rates of 13 per cent and 69 per cent in groups of 11 and 16 patients respectively. In an earlier study from St. Mark's Hospital, Wolfe and Bussey reported crude 5-year survival rates of 21·3 per cent for synchronous and 45·5 per cent for metachronous lymphadenopathy[15]. In the present study, however, this difference was not found. Although the total number of cases with histologically proved synchronous inguinal metastases was small (nine patients), five survived after treatment for 5 years. Perhaps this difference can be accounted for by different proportions of fixed advanced lymphadenopathy in the various series but clinical information is not available to determine this point. It may be, however, that a policy of initial biopsy of an enlarged node allows patients with early metastatic disease to be identified before their presentation with metachronous lymphadenopathy such that immediate treatment improves prognosis.

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Management of thyroglossal cysts in children

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Forty children with a suspected thyroglossal cyst were operated on by one paediatric surgeon receiving primary and secondary referrals in an 8-year period. Nine patients (22 per cent) proved to have other pathology. Multiple operations were required in eight of 17 patients (47 per cent) who had infected thyroglossal cysts but in only one of 14 (7 per cent) with uninfected cysts. In the infected group preliminary incision and drainage was necessary in five cases and cyst recurrence occurred in four (24 per cent), whereas in the uninfected group there was only one recurrence (7 per cent) in a patient with double pathology. Infection and recurrent cysts were the chief reasons for multiple operations. Recurrence was caused by inadequate performance of the correct operation (Sistrunk's) or choice of the wrong operation. Two of our own three recurrences were due to the latter, other pathology being suspected intraoperatively. Histological study of the specimens showed that thyroglossal ducts were frequently multiple and widely spaced. In children any lesion whose presentation is typical of a thyroglossal cyst should be treated with an early Sistrunk's operation. The operation in children who have other pathology has no complications and is justified.

Keywords: Thyroglossal remnants, child

Thyroglossal cysts are the commonest cause of midline neck swellings between the ages of 6 months and 15 years[1]. The surgeon's main aim is to perform one adequate operation and avoid recurrence, which is said to be commoner in children than in adults[2].

The majority of thyroglossal cysts lie close to the hyoid bone, though they may be at any site along the pathway of descent of the thyroid anlage The hyoid fuses anteriorly in the sixth gestational week and may include remnants of the thyroglossal duct[1,3].

Howard and Lund[4] have recently emphasized the importance of adequate neck dissection for thyroglossal remnants, in order to avoid an incomplete operation. Excision of the central portion of the hyoid bone and dissection of the thyroglossal duct was first described by Shlange[5] in 1893. Sistrunk[6] popularized the operation in 1920, advising excision of a quarter of an inch (0·63 cm) of mid-hyoid bone and a cuff of muscle an eighth of an inch (0·32 cm) wide around the duct to prevent it fragmenting before the back of the tongue was reached. Attention has been drawn to the fact that the duct is frequently multiple and branched[7,8]. Mickel and Calcaterra[9] even proposed modifying Sistrunk's operation to involve a wider anterior neck dissection in adults, removing 3–4 cm of central hyoid bone and a 2–3 cm core of muscle up to the foramen caecum.

Infection is a second factor predisposing to multiple operations[10].

Patients and methods

The case notes were reviewed of all children with a midline cervical swelling presenting to one paediatric surgeon from January 1980 to December 1987. Thirty-seven patients were primary referrals and three were secondary referrals having had previous surgery.

The following information was recorded: sex, age at presentation, length of history, mode of presentation, preoperative investigations, operations performed and operative findings, histology of the lesion, postoperative complications, length of follow-up, and final outcome.

It was not our policy to carry out radioactive iodine isotope scans routinely.

The routine histological sections consisting of representative samples from each specimen were reviewed. The criteria for diagnosis were the presence of ductular or cystic structures lined by simple cuboidal or columnar epithelium, or non-keratinizing stratified epithelium without the epidermal appendages Additional findings recorded were the presence of associated minor mucous glands, lymphoid elements and thyroid acini.

Results

There were 40 children whose ages at presentation ranged from newborn to 11 years with a mean age of 3·8 years. Of the 31 children with thyroglossal cysts, there were 15 boys and 16 girls. The nine with other pathology included seven girls and two boys.

The length of follow-up ranged from 4 months to 6 years 6 months, with a mean of 2 years 8 months. There was one postoperative wound infection with *Staphylococcus aureus*

Children with infected thyroglossal cysts

An infected thyroglossal cyst (*Table 1*) was present in 17 children. The mean length of history was 5·4 months. All the lesions were in the midline except one, which was a discharging sinus to the left of the midline.

Seven were enlarging or erythematous neck swellings, three were abscesses, and seven were discharging sinuses of which four were spontaneous and three postoperative.

Five of these children had had an upper respiratory infection shortly before presentation.

Multiple operations were carried out in eight of these patients (47 per cent); five children had two operations, two had three operations and one required four operations. Incision and drainage was necessary before definitive surgery in five patients. Recurrence occurred in four children: two referred from elsewhere and two of our own. One of our recurrences followed a simple excision, when the lesion at operation appeared not to be a thyroglossal cyst, and three recurrences followed definitive surgery.

Children with uninfected thyroglossal cysts

Fourteen children presented with uninfected thyroglossal cysts (*Table 2*). None had had a recent respiratory tract infection. The mean length of history was 7·5 months.

Thirteen children had a Sistrunk's operation initially. One

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Table 1 *Patients with infected thyroglossal cysts*

	Sex	Age (years)	Preceding infection*	Operation 1	2	3	4	Recurrence	Histology
Erythematous enlarging swellings									
1	F	4		S					TGC
2	F	8		S					Inf.
3	M	5	+	S					TGC
4	M	4	+	S					TGC
5	F	5	+	E	S			+	TGC
6	F	5		(S)	S			(+)	TGC
7	F	4		S					TGC
Abscesses									
8	M	3		I and D	S				TGC
9	F	1	+	I and D	I and D	S			Inf
10	M	2	+	I and D	S				TGC
Discharging sinuses									
11	M	1		S	S			+	TGC
12	M	3		S					TGC
13	F	6		(I and D)	(I and D)	I and D	S		TGC
14	M	(6 months)		(I and D)	(S)	S		(+)	TGC
15	F	8		S					TGC
16	F	9		S					Inf
17	M	1		S					TGC

* Preceding upper respiratory infection S, Sistrunk's operation; TGC, thyroglossal cyst, Inf., infected with no definitive histology, E, excision, ( ) treated elsewhere; I and D, incision and drainage

Table 2 *Patients with uninfected thyroglossal cysts*

	Sex	Age (years)	Operation 1	2	3	4	Recurrence	Histology
18	M	5	S					TGC
19	M	9	S					TGC
20	F	1	S					TGC
21	M	2	S					TGC
22	M	(6 weeks)	E	E	S		+	TGC and D
23	M	3	S					TGC
24	M	5	S					TGC
25	M	9	S					TGC
26	M	(9 months)	S					TGC
27	F	5	S					TGC
28	F	1	S					TGC
29	F	2	S					TGC
30	F	4	S					TGC and D
31	F	2	S					TGC

S, Sistrunk's operation, TGC, thyroglossal cyst, E, excision; D, dermoid cyst

(No. 30) was a 4-year-old girl with double pathology: a ruptured dermoid cyst and a thyroglossal cyst.

The only recurrence was in a patient (No. 22) who did not have a Sistrunk's operation initially, but had a simple excision twice for an apparent dermoid cyst Only after a Sistrunk's operation on the third occasion was it demonstrated that a thyroglossal remnant and a dermoid cyst were both present.

Patients presenting at birth with midline cervical pathology

Patient No. 22 had a 1-cm fluctuant swelling operated on at 6 weeks of age. No. 17 discharged milky fluid intermittently from a submental sinus when feeding, and at 10 months presented with an infected swelling. A sinogram showed a cyst at the base of the tongue communicating with a second cyst adjacent to the hyoid bone, which proved to be thyroglossal remnants after Sistrunk's operation. A patient aged 2 years had a dermoid cyst, and No. 19, aged 9 years, had a thyroglossal cyst removed at Sistrunk's operation.

Histopathology

In 28 cases evidence of a thyroglossal remnant was present. In six of these, inflammation was heavy though some thyroglossal elements were recognizable. In three cases, chronic inflammation obscured any pre-existing structures and so the diagnosis of thyroglossal remnant could not be made (*Table 1*: designated as infected). In two, both a thyroglossal remnant and a dermoid cyst were present.

In the cases diagnosed as thyroglossal cysts by the criteria previously described, the number of epithelial lined structures varied from a solitary cyst up to one with 20 separate ductules, which were found in groups often widely dispersed along the hyoid bone and in the surrounding striated muscle (*Figure 1*). Most of the specimens showed multiple ducts. In the three cases that recurred after Sistrunk's operation, the number of ducts present were 1, 15 and 20 respectively, which was a similar range to that seen in the non-recurrent group. The mean length of hyoid resected was 15 mm. Associated minor mucus glands were present in 18 out of 28 cases and were numerous in seven. Thyroid tissue was present in ten cases.

Patients with other pathology

Histology and microbiology of the remainder revealed five dermoid cysts, one fibromatosis and three lymph nodes, one a case of chronic lymphadenitis from which *Mycobacterium avium*

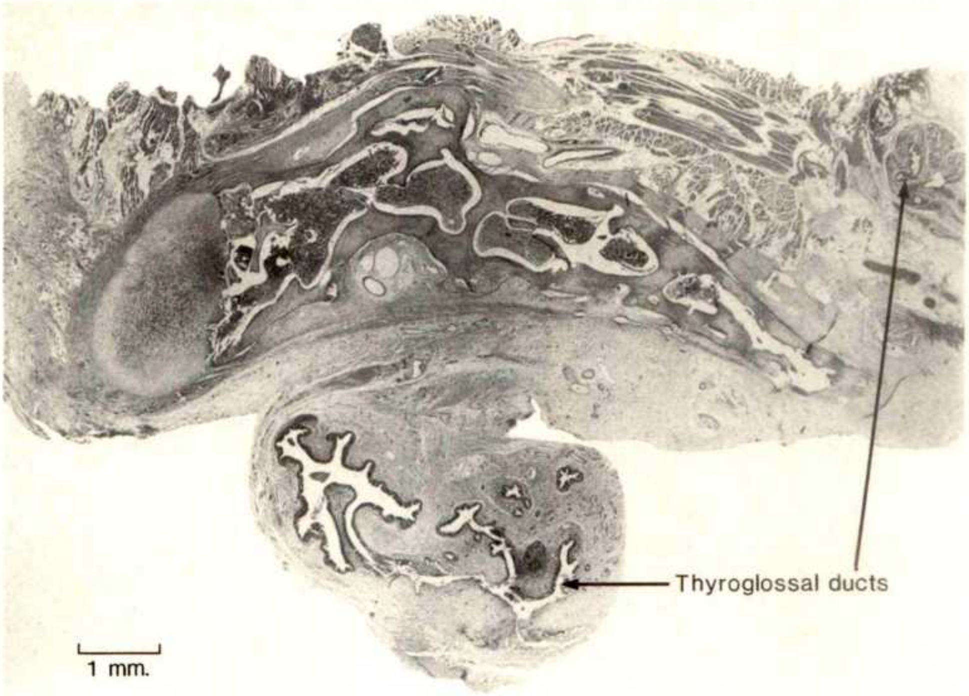

Figure 1 *Excised segment of hyoid bone with thyroglossal duct remnants close to resection margin; magnification × 15*

intracellulare scrofulaceum (MAIS) was cultured. Seven had a Sistrunk's operation and two had simple excision.

Discussion

It is of value to present the group of 40 children as a whole because the nine with diagnoses other than thyroglossal cysts were indistinguishable preoperatively and sometimes peroperatively. In a large paediatric series, 31 per cent had other pathologies[8], which required surgery. Dermoid cysts are the second most common cause of midline neck swellings in children[1] and should be excised because they can become infected. The fibromatosis required complete excision and the recommended treatment for a node infected with atypical MAIS[11] is also removal.

Preoperative diagnostic difficulty occurred when the swelling was off the midline. In this series two out of 31 cysts (6 per cent) were off the midline, both to the left of the midline; this was similar to the findings in other series[12]. In a 1-year-old child the lump was initially so hard that the child was investigated for a malignant tumour. The second child, aged 9 years, had a spontaneously discharging sinus which had been present for 2 years.

In the girl with the MAIS-infected node, its cystic nature and midline position at the level of the hyoid mimicked a thyroglossal cyst. Movement of the lump on tongue protrusion can be an unreliable sign, especially in the newborn and infants, although dermoid cysts are said not to move on tongue protrusion[1].

In this series two of four children noted to have midline neck swellings at birth had dermoid cysts present, and three had a thyroglossal cyst present, one having double pathology. At this age other diagnoses must be considered, such as cystic hygroma, cavernous haemangioma, teratoma, thyroid hyperplasia and ectoptic thyroid tissue.

The two reasons for multiple operations were infection and inadequate surgery, either the correct operation inadequately performed or the wrong operation being chosen. Infection was associated with multiple operations because of the need for an initial incision and drainage procedure. Often these children have an upper respiratory tract infection in the 2 weeks before the cyst becomes inflamed and symptomatic. One girl required two drainage procedures in 2 months because the opportunity was missed to operate as soon as she became infection-free after the first operation. Also, infection contributes to recurrence by making the tract difficult to locate and by obscuring anatomical landmarks[10].

This was a factor in patient No. 11 who had a discharging sinus and was our one recurrence after 31 Sistrunk's operations (3 per cent). Another factor was our approach to the cyst, which was situated at the level of the thyroid cartilage. A low cervical incision made dissection to the back of the tongue difficult. It would have been easier to trace the tract through two incisions, one over the cyst and one over the hyoid[12].

The two other recurrences in our hands were caused by choosing simple excision to remove a lesion which appeared not to be a thyroglossal cyst at operation. Our overall recurrence rate for thyroglossal remnants was therefore three in 31 children (10 per cent). It needs to be emphasized that the surgeon should avoid a simple excision when the original presentation of the condition is typical for thyroglossal cyst, whatever the appearances at operation. We recommend a Sistrunk's operation for the majority of patients who have other pathology as there were no complications in these patients.

In the three children initially operated on elsewhere, inadequate excision was the cause of recurrence. In one (No. 13) no attempt at excision was made, in the second (No. 14) the mid-hyoid bone had not been excised, and in the third (No. 6) the tract was not traced to the root of the tongue. There is no question that Sistrunk's operation is the treatment of choice for thyroglossal cyst[13].

Histopathological examination revealed that multiple ducts can be widely spaced. We have assumed that 15 mm of central hyoid bone is adequate, although *Figure 1* shows how close excision margins may be to multiple ducts.

Successful surgical mangement of thyroglossal cysts in children requires intervention as soon as possible after presentation to avoid infection. If there is doubt about the diagnosis, the authors recommend a radical Sistrunk's operation in the first instance, as the thyroglossal tract is not always visible to the naked eye, the tract is often multiple, and there may be double pathology.

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Use of an embolectomy catheter to remove a submandibular duct stone

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Traditionally, stones in the submandibular duct have been removed transorally if the stone is anterior to the posterior border of the mylohyoid muscle. If the stone is posterior and therefore impalpable, most texts recommend excision of the gland[1,2]. In most cases of duct stones, removal of the gland is not necessary as 75 per cent of glands function normally when a stone has been removed[3]. When removing stones transorally, it is important to insert a stay suture behind the stone before any manoeuvre is carried out, to prevent displacement into the gland. We describe a method for recovering such stones.

Patients and methods

A 26-year-old woman presented with a 4-month history of recurrent swelling in the left submandibular region after meals. On examination there was a stone palpable intraorally, and a sialogram confirmed the presence of the stone in the intraoral part of the duct. Although palpable preoperatively, the stone proved difficult to feel at operation under general anaesthesia. A stay suture was inserted behind the probable location of the stone. The duct was probed and an incision was made on to the probe. After a thorough exploration and examination, it was concluded that the stone had slipped back. A size 2 embolectomy catheter was inserted into the duct and passed posteriorly. The balloon was inflated, the catheter was slowly withdrawn and a 2-mm stone was recovered. Following the operation, the patient was asymptomatic.

Discussion

Balloon catheters have been used for a variety of reasons such as the removal of bile duct stones[4], removal of tracheobronchial or oesophageal foreign bodies[5], and to stem bleeding from an endobronchial biopsy site[6], but this is the first report of the use of the balloon catheter to recover salivary duct stones. We present this as a useful method for removing stones that migrate during attempted transoral removal or for small stones that lie posteriorly, in order to avoid the need for gland excision.

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Chronic intussusception in children

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Nine children presented with intussusception lasting for 14 days or more. Their mean age was 8·5 years. Diagnosis of intussusception was delayed considerably, probably due to an unusual presentation. Compared with acute intussusception, symptoms consist of infrequent attacks of abdominal pain, sporadic vomiting and no, or small, changes in defecation. Marked weight loss and an abdominal mass assume diagnostic significance, in contradiction to bloody stools. Ultrasonography can be of diagnostic value. An attempt at hydrostatic reduction is often unsuccessful. A high frequency of organic lesions precipitating intussusception warrants early surgical intervention.

Keywords: Intussusception, children

Intussusception is considered to be a readily diagnosed disease because the classical clinical pattern of colicky abdominal pain, vomiting and bloody stools in a child under 2 years of age is well recognized. However the fully developed triad of cardinal symptoms has been noticed in less than 50 per cent of cases[1,2]. The presence of symptoms depends on the degree of strangulation of the bowel.

In the absence of strangulation, currant-jelly stools and vomiting (due to intestinal obstruction), abdominal distension, abnormal bowel sounds and constipation may be absent. A non-strangulating intussusception may reduce spontaneously if not protruded too far or may strangulate if it progresses. It may also stay unchanged for several days or even months. In the past intussusceptions lasting for 14 days or more have been considered to be chronic[4–6]. They are distinguished from acute forms of intussusception by a characteristic clinical pattern that is conducive to delay in diagnosis. This paper reports the clinical pattern in, and diagnostic features of, nine cases of chronic intussusception in children.

Patients and methods

The reports of all 139 patients under the age of 15 years admitted to the Department of General Surgery of the St. Canisius-Wilhelmina Hospital or to the Pediatric Surgical Centre of the St. Radboud Hospital of the Catholic University of Nijmegen from 1968 to 1988, in whom the clinical diagnosis of intussusception was supported either by radiological evidence or by laparotomy, were studied retrospectively. Nine patients had a chronic intussusception as defined above.

Results

The mean age was almost 8·5 years for the seven male and two female patients (range from 3 years and 3 months to 14 years and 2 months). Three had an intussusception of the enteric type and three were ileoileocolic intussusceptions. Two were of the ileocaecal type and there was one appendicocaecocolic intussusception. In six cases a leading point was found. All nine patients had complained of daily intermittent abdominal pain. In eight of nine cases the frequency of the attacks was five times a day or less. Seven patients vomited (also sporadically). Two patients lost blood per anus. One patient complained of constipation. In three cases a looser stool or diarrhoea was produced at a normal frequency. In five cases there was no change in defaecation. Six patients were anorexic. On physical examination the weight of three patients was below the tenth percentile and in five cases between the tenth and 50th percentile. Signs of intestinal obstruction, abdominal distension and abnormal bowel sounds were found in four cases. An abdominal mass was present in seven patients.

The mean time between the onset of symptoms and admission was 35 days ranging from 3 to 93 days. A chronic intussusception was suspected because of the continuing presence of symptoms and ill health of all children. In three cases there was a considerable delay in diagnosis of 7, 9 and 13 days after admission. In the last two of these cases diagnosis at admission was of an appendix mass. In eight cases diagnosis was reached preoperatively: by clinical presentation (two cases), by barium enema examination (three cases), by small bowel follow-through meal (one case) and by ultrasonography (two cases). A plain abdominal radiograph of three patients showed air–fluid levels in dilated bowel loops on the day the diagnosis of intussusception was reached.

All children were operated on. An attempt at hydrostatic reduction was made in four cases but without success. In three of these cases an organic lesion was found. At laparotomy the fourth case was found to have undergone reduction. Although, retrospectively, an intussusception could also be seen on an earlier barium enema, this was the only case where a recurrent acute intussusception could not be ruled out with certainty. In four patients manual reduction was performed easily, in one case followed by enterotomy and in another by a small resection of viable jejunum because of a tumour which turned out to be a fibroid polyp. In two cases with a duration of 93 and 56 days manual reduction could only be achieved with great difficulty because of adhesions after which ileocaecal resection was done because of questionable viability. Partial ileal resection without manual reduction, because of possibly non-viable bowel, was performed in two cases with a duration of 16 and 21 days.

Discussion

Strangulation of the bowel can occur early or late in the course of an intussusception. An intussusception lasting more than 14 days is an uncommon condition. The incidence is estimated at 5 per cent of all intussusceptions. Under the age of 2 years, when most acute intussusceptions happen, an incidence of 3 per cent has been calculated while over that age it was 10 per cent[7]. This suggests that at an older age the anatomy allows an intussusception to occur without any significant impairment of the blood supply. On the other hand the possibility remains that delay in diagnosis, caused by the older age of the child, permits a non-strangulated intussusception to last more than 14 days.

Chronic intussusceptions distinguish themselves from acute intussusceptions by less severe abdominal pain and vomiting, a lower percentage of rectal bleeding and a higher percentage of diarrhoea[1–3,5,7]. A striking feature is the significant weight loss in many children with chronic intussusception due to long-standing anorexia and nausea or to the underlying causative factor involved[5,7].

In addition to small bowel follow-through and barium enema, ultrasonography can be of diagnostic value particularly when a mass is found[5,8–11]. The sonographic picture of intussusception is characteristic. A cross-section through the

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apex shows a target-like pattern. Scanning through the more proximal intussuscepted bowel demonstrates an image composed of two concentric rings and an inner circular area. Scans along the longitudinal axis exactly through the centre of the intussusceptum show four parallel stripes of low echogenity, delineating three reflective areas. Longitudinal scans not through the centre of the intussusceptum demonstrate three stripes of low echogenity separated by two hyper-reflective stripes.

Attempts at hydrostatic reduction of chronic intussusceptions have not been very successful in the past[5,12]. The high incidence of organic lesions is another reason for early surgical intervention, the more so as in older children this organic lesion sometimes turns out be a lymphoma[12]. At laparotomy manual reduction can often be done with ease[5,12]. In the case of irreducibility, questionable viability of the bowel and suspicion of intramural pathology, resection is indicated.

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Surgical workshop

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Surgical treatment of carcinoma involving the vagina

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When tumours of the vagina or tumours of the uterine cervix involving the vagina are treated by operation, it is often necessary to excise a substantial part of it producing subsequent sexual problems. Attempts to create a new vagina by skin grafts[1,2] and amnion[3] have had some degree of success and there have been some favourable reports of using the sigmoid colon for this purpose[4,5]. When tumours involving the vagina are extensive, the operation may involve an even wider excision removing the bladder and urethra (anterior pelvic clearance). After cystectomy, the ureters are transplanted into an isolated loop of bowel. This has usually been a piece of ileum but sigmoid colon can be used for the conduit. We have found that it is possible to use sigmoid colon to create a new vagina and to create a urinary conduit in the same patient. The operation is described with the initial experience.

Surgical technique

The operation is carried out through a vertical, midline incision extended to the left of the umbilicus into the upper abdomen. The anterior or central clearance is performed with dissection from both the abdominal and perineal aspects but the vulva and vestibule are left *in situ*. The left colon is fully mobilized up to and including the splenic flexure, carefully preserving the blood supply. Two isolated loops of sigmoid colon are fashioned, preserving the sigmoid branches from the inferior mesenteric artery (*Figure 1a*). The mesosigmoid is split in a fan-shaped manner down to the stem of the inferior mesenteric artery, dividing the marginal artery in three places but ensuring that there is a feeding sigmoid branch into each of the two proposed loops (*Figure 1b*). The bowel is divided near the junction of the descending colon and the sigmoid at the rectosigmoid junction and at some convenient point in the mid-sigmoid (*Figure 1c*). The two isolated loops thus prepared are displaced to the right; bowel continuity is re-established by end-to-end anastomosis.

The lower loop is used to create the new vagina. The end is grasped by tissue forceps passed up from the perineal wound. The perineal operator draws the loop down and sutures it to the introitus with absorbable sutures (Vicryl®, Ethicon Ltd., Edinburgh, UK). The upper end of the loop is closed.

The upper loop is used as the urinary conduit, the ureters are anastomosed to its proximal end and the distal end is brought out through the right rectus and is sutured to the skin of the right iliac fossa as a urinary stoma.

Results

This operation has been undertaken on five patients. There was no significant early postoperative morbidity. The urinary loop functions satisfactorily and there is normal renal function. The new vagina has remained of adequate calibre but dilatation has been required in one patient. Sexual function is satisfactory in three of the five patients. One patient has not, as yet, undertaken sexual activity and one patient had early tumour recurrence and never 'used' the neovagina.

Discussion

This operation offers advantages to young women who need a radical anterior pelvic clearance including excision of the vagina. In particular, reconstruction of the vagina is immediate, without adding to the severity of the operation because some bowel has to be mobilized and isolated to fashion the urinary conduit. Although transplantation of the ureters into the intact colon may cause severe metabolic problems, this does not pertain to the transplantation of the ureters into a short isolated segment of colon used as a conduit[6]. A short, detached loop of ileum or colon is equally effective in carrying the urine to

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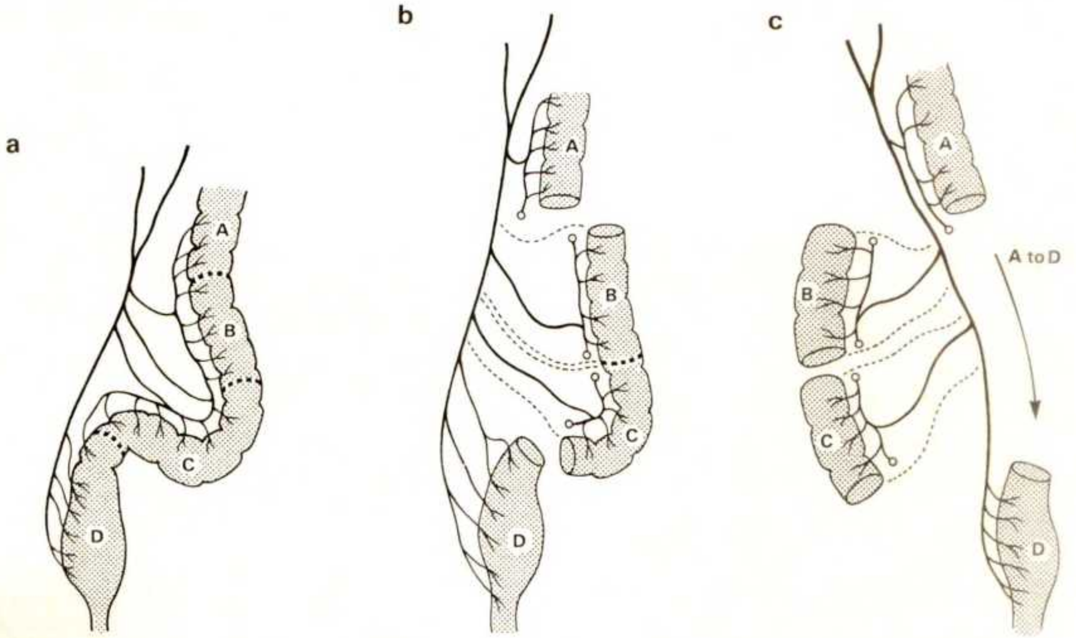

Figure 1 **a** *The sigmoid colon with its blood supply, showing the points of section:* **b** *note the preservation of the blood supply to produce two loops for the neovagina and urinary conduit.* **c** *The loops are separated; the large bowel is reanastomosed*

the skin surface from the transplanted ureters[7]. Because the colon rather than the ileum is used for the isolated conduit, there is only one intestinal anastomosis instead of two, which may well reduce the hazard of surgery. It may be argued that a colorectal anastomosis would be more hazardous than using an ileal anastomosis but this is not our experience. In expert hands, the risk of leakage from either type of anastomosis is very low[8].

There are several previous reports of employing colon to fashion a vagina for congenital absence of the structure; the results of these procedures confirm that the colon makes a satisfactory and usable vagina[5,9]. Previous experience indicates that a colonic loop makes an acceptable substitute for the vagina but the cases reported here show that it is possible to fashion a urinary conduit and a vagina from the sigmoid colon while carrying out a primary colorectal anastomosis.

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Pelviureteric junction obstruction and recurrent abdominal pain in childhood

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Three cases of recurrent abdominal pain due to pelviureteric junction obstruction in childhood are presented. Ultrasound is useful in confirming the diagnosis and pyeloplasty is recommended.

Keywords: Abdominal pain, pelviureteric obstruction, childhood

More than 10 per cent of children complain of recurrent abdominal pain but few will have organic pathology. Pelviureteric junction obstruction was shown to be the cause in one of 100 such children studied by Apley[1]. Conversely, only one of 32 children with pelviureteric junction obstruction reported by O'Donnell had a history of recurrent abdominal pain[2]. These texts may give the impression that this mode of presentation is rare in children, resulting in clinicians failing to consider the diagnosis. Three children with recurrent abdominal pain and pelviureteric obstruction are presented to illustrate the problems of diagnosis and a policy of investigation of children with recurrent abdominal pain is suggested.

Case reports

Case 1

A boy aged 5 years presented with a 2-day history of severe abdominal pain and constipation. He had suffered from similar attacks of short duration during the previous 3 years. Investigations carried out elsewhere included an intravenous urogram which showed fullness of the left renal pelvis. The attacks usually followed a meal accompanied by fluids and had been attributed to intolerance to artificial food colourings. He had tachycardia but was apyrexial. There was tenderness and a suggestion of a mass in the left hypochondrium which was confirmed by abdominal X-ray. Urine microscopy showed occasional leucocytes and red cells but culture was sterile. Ultrasound examination revealed a large left renal pelvis and thinned renal parenchyma without dilatation of the ureter. At operation a fibrous stricture of the upper ureter was resected and continuity restored with an Anderson–Hynes pyeloplasty. An isotope scan carried out 6 months after the procedure showed no evidence of obstruction and he is asymptomatic.

Case 2

A 5-year-old boy presented with abdominal pain and vomiting of 24-h duration. The pain was localized to the left side of the abdomen. In the past his general practitioner had described him as 'a difficult child with recurrent bouts of abdominal pain and vomiting'. He had attended a casualty department on several occasions during a period of 2 years. When referred to a paediatrician his symptoms were attributed to reactive hypoglycaemia but this was never substantiated. He was afebrile and there was left sided abdominal tenderness. Urine microscopy and abdominal X-ray were normal. A limited intravenous urogram showed no function on the left side and ultrasound demonstrated a left hydronephrosis without dilatation of the ureter. At operation the diagnosis of pelviureteric junction obstruction was confirmed and an Anderson–Hynes pyeloplasty was performed. An isotope scan 6 months later showed equal function and no obstruction to either kidney. He remains asymptomatic.

Case 3

An 8-year-old boy complained of abdominal pain and vomiting for 24 h. He had had episodes of pain with vomiting over a period of 2 years. At the onset of his symptoms he had been admitted to hospital elsewhere and had been seen twice in the paediatric clinic of a second hospital in the 6 months before admission to our unit. His pain was ascribed to constipation, although his bowel habit was described as 'fairly regular'. He was pyrexial and moderately dehydrated. There was a large, tender mass on the left side of his abdomen. Ultrasound showed left hydronephrosis without a dilated ureter. Urine microscopy was normal. Intravenous antibiotics were started and he underwent Anderson–Hynes pyeloplasty for pelviureteric junction obstruction. He remains asymptomatic 10 months after operation and isotope excretion study shows no obstruction and good function.

Discussion

All three boys had experienced abdominal pain and vomiting for a number of years and, despite hospital consultations, unsubstantiated diagnoses had been made. Abdominal pain accompanied by non-bilious vomiting occurs in urinary tract disease and the child with pelviureteric junction obstruction may present with severe acute abdominal pain, haematuria or infection, but intermittent pain associated with vomiting is also recognized[3,4]. Therefore, abdominal ultrasound is indicated or, if this is unavailable, intravenous urography[5]. If these tests demonstrate hydronephrosis without a dilated ureter, an isotope excretion study may be helpful in establishing the diagnosis of pelviureteric obstruction and comparing the function of the kidneys.

Lateral abdominal pain may indicate important pathology in the urinary tract or, less commonly, the spleen (if left sided) or the gallbladder (if right sided). Rarer causes include adrenal tumours, especially neuroblastoma, retroperitoneal cysts and pseudocysts and, even more uncommonly, intestinal ulceration from ectopic gastric mucosa within intestinal duplication cysts or diverticula. Metastatic abscesses may occur within the iliacus or psoas muscles and are more common in recent immigrants from Africa or Asia. In this context, Apley has coined the aphorism 'The further the localization of the pain from the umbilicus, the more likely is there to be an underlying organic cause'[1]. It should be remembered, however, that young children do not localize pain well.

Recurrent abdominal pain with bilious vomiting is of great importance and all affected children should undergo barium meal examination to exclude intestinal malrotation predisposing to intermittent midgut volvulus[6]. Failure to appreciate the significance of these symptoms may result in intestinal infarction. Other causes of recurrent pain of intestinal origin include Crohn's disease and *Ascaris lumbricoides*, the latter occurring most frequently in recent immigrants.

Recurrent abdominal pain, with or without vomiting, headache or pyrexia, is common in children. Such pain is usually felt centrally, about the umbilicus, and may be a response to stress at home or school. The child may be setting unattainable standards for himself or be under pressure to achieve beyond his abilities. It may be impossible to identify a psychological cause for the pain but the 'periodic syndrome' may be diagnosed where emotional disturbance is strongly suspected[1].

These case histories support the use of ultrasonic examination of the abdomen, to be repeated if necessary, in all children

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with recurrent abdominal pain accompanied by non-bilious vomiting. This is especially important in children with left sided pain because of the predominance of left sided pelviureteric obstruction[3]. Barium meal is the investigation of choice when the vomitus contains bile. Any diagnosis of psychological or organic cause should be based on strong clinical grounds or on the results of specific investigations.

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Case report

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Multiple primary retroperitoneal tumours: a unique case

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Primary tumours arising in the retroperitoneal space are uncommon and retroperitoneal neurilemmomas (or schwannomas) are particularly rare[1]. Pack *et al.*[2] reported only one in 120 cases of primary retroperitoneal tumours, Donnelly[3] reported one in 95 cases, Felix *et al.*[4] reported two in 53 cases and Braasch and Mon[5] encountered none in the Lahey Clinic experience between 1930 and 1960.

We report the first case, as far as we are aware, of metachronous primary retroperitoneal neurilemmomas: that is, tumours occurring in different retroperitoneal sites of the abdomen and pelvis at different times.

Case report

The patient, a 47-year-old white caucasian man, presented initially as an emergency, with central lower abdominal pain, right shoulder tip pain, dysuria and recent 1-stone (6·4 kg) weight loss. On examination there were signs of peritonitis and a large, hard, irregular mass arising from the right side of the pelvis. No stigmata of von Recklinghausen's neurofibromatosis were apparent. Laparotomy revealed a haemoperitoneum and a hard, nodular tumour, 14 × 10 cm, arising from the right lateral wall of the pelvis. There was no evidence of local invasion, and venous bleeding was profuse. The tumour was removed and histology revealed low grade sarcomatous change in a neurofibroma.

The patient remained well and was discharged from follow-up after 3 years. He re-presented, again as an emergency, at the age of 56 years, with an identical history and similar signs to his previous presentation. On this occasion the mass was palpable suprapubically and rectally. At laparotomy there was a tumour, 16 × 10 × 10 cm, in the central pelvis adjacent to the bladder and rectum. It was well encapsulated and mobile. Histology was reported as practically identical to the previously excised tumour but it was considered to be a malignant fibrous histiocytoma. The patient was now followed up with regular 6-monthly abdominal and pelvic ultrasound examinations.

At the age of 63 years, 16 years after he originally presented, a 5-cm mass in the left side of the pelvis was detected on ultrasound examination. A computed tomographic scan (*Figure 1*) revealed this to be 4·5 cm in diameter, lobulated and situated in the posterolateral pelvis, separated from the bladder by a fat plane. The tumour was excised at laparotomy and reported to be a low grade fibrosarcoma, identical to previous excisions, and not a malignant fibrous histiocytoma, owing to the lack of pleomorphism.

Eighteen months later, at the age of 64 years, a follow-up ultrasound showed a 7-cm mass inferior to the left kidney. This was confirmed by computed tomographic scan (*Figure 2*). At laparotomy, a 10-cm spherical tumour, posterior to the splenic flexure and inferior to the spleen, was completely excised. After extensive pathological discussion the tumour was now thought to be a cellular schwannoma, because it was a spindle cell tumour with mild pleomorphism, no necrosis and occasional mitotic figures with predominant Antoni A areas lacking cellular palisading and Verocay bodies (*Figure 3*). In addition, immunocytochemical staining with S100 protein showed patchy positivity consistent with the diagnosis. On review, histologies were identical.

Discussion

Following an extensive literature search we have been unable to find a case of multiple primary retroperitoneal tumours occurring at different sites within the abdomen and pelvis. Malignant retroperitoneal tumours are four times more prevalent than benign tumours[6]. The neurilemmoma is a benign tumour with a well defined form that resembles neoplasms of fibroblastic origin. The tumours removed in this patient were not recurrences because they were in different sites in the retroperitoneum, well encapsulated and completely excised, with no gross or histological evidence of invasion. Most patients with a solitary neurilemmoma are young to middle-aged adults[7]. Our patient was aged 47 years on initial presentation.

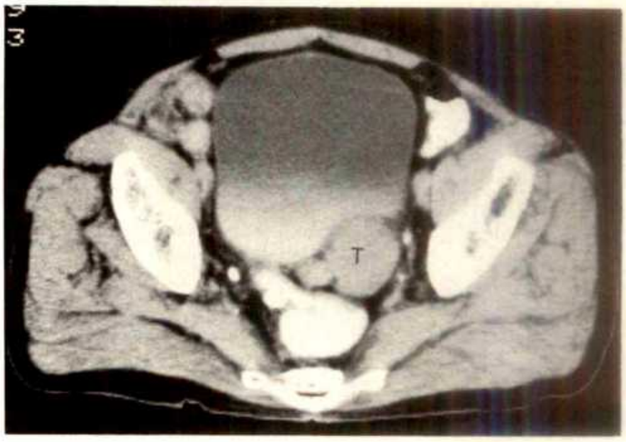

Figure 1 *Computed tomographic scan showing a 4·5-cm lobulated mass (T) on the left side of the pelvis, separate from bladder*

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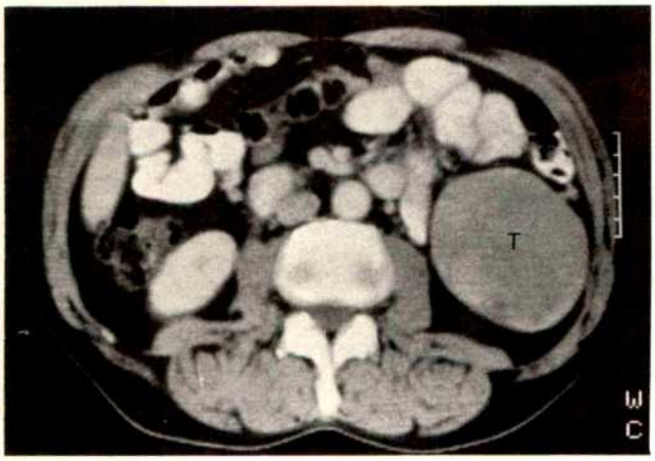

Figure 2 *Computed tomographic scan showing a 7-cm mass (T) inferior to the left kidney*

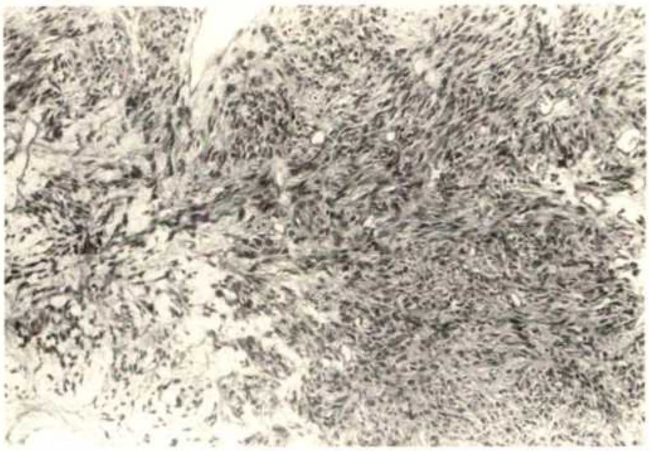

Figure 3 *Photomicrograph showing a whorled pattern of highly cellular spindle cell areas within the tumour but adjacent less-cellular areas with a myxoid stroma are also seen (× 25). Tumour removed when patient aged 64 years*

There are only 42 reported cases of retroperitoneal neurilemmoma in the literature[8]. None of these was multifocal. A high proportion of solitary neurilemmomas occur in the region of the head and neck, especially the spinal nerve roots, acoustic nerve and other cranial nerves[8]. In the present case all the lesions were retroperitoneal and there was no evidence of lesions elsewhere.

The diagnosis of von Recklinghausen's neurofibromatosis was discounted because the patient had none of the stigmata seen in the recognized different forms of neurofibromatosis[9]. The terminology of peripheral nerve sheath tumours has been confused by the interchangeable use of neurilemmoma, neurofibroma, schwannoma and neuroma. Current opinion believes that the neurilemmoma (or schwannoma) and the neurofibroma are separate histological and clinical entities, although their cell of origin in both cases is the Schwann cell[1].

The histopathological diagnosis of cellular schwannoma was reached after careful review of all the sections. This is a variant of neurilemmoma that has been reported by Woodruff *et al.*[10], and more recently by Fletcher *et al.*[11]. Both groups noted that it may be mistaken for a malignant tumour[10,11]. This is substantiated by our case, diagnoses of low grade fibrosarcoma and malignant fibrous histiocytoma having been made before the final diagnosis was reached. However, before Woodruff and Fletcher no classification of cellular schwannoma actually existed and at the time of this patient's initial presentation these tumours were considered to be low grade fibrosarcomas. Cellular pleomorphism is not by itself an indication of malignancy in neurogenous tumours[1]. In Woodruff's series[10] of 14 cellular schwannomas, six had been mistaken for either malignant fibrous histiocytoma, leiomyoma or sarcoma, but follow-up has so far shown the tumour to behave in a benign fashion. Similarly, five of the 18 cases in the series of Fletcher *et al.*[11] had previously been diagnosed as sarcomas.

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Surgical management of neutropenic enterocolitis

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Three cases of histologically confirmed neutropenic enterocolitis, each presenting as an acute abdomen in patients with leukaemia are presented. All three patients presented with fever and abdominal pain within 14 days of completing a course of chemotherapy. Signs of peritonitis localized to the right iliac fossa developed in each patient, in spite of aggressive antibiotic therapy and bowel rest. All three patients were found to have non-viable caecum at laparotomy and were treated by right hemicolectomy. Primary ileocolic anastomosis was performed in one patient, who recovered following a stormy postoperative course owing to sepsis. Two patients underwent formation of an ileostomy with distal mucous fistula and each recovered with minimal postoperative complications; secondary anastomosis was performed electively in both cases. The difficulty in diagnosing neutropenic enterocolitis preoperatively is discussed and the place of non-operative management is reviewed but we recommend surgical intervention as a means of ensuring removal of a localized septic focus until marrow regeneration occurs.

Keywords: Colitis, leukaemia, neutropenia

In the last two decades the aggressive use of multiagent chemotherapy has prolonged the survival for many patients with haematological malignancy[1]. As a result, new complications of both the disease process and the treatment employed are presenting for management. Neutropenic enterocolitis (also known as typhlitis[2], ileocaecal syndrome[3] and necrotizing enteropathy[4]) is a life-threatening condition from which, until 1979, only two patients had survived[5,6]. While current series quote a survival rate of 50–80 per cent[7–9], no clear management policy has been established. Neutropenic enterocolitis has been reported in patients with acute leukaemia[2,3,8], aplastic anaemia[9], cyclic neutropenia[10,11] and (rarely) solid tumours[4], and it may present to surgeons working in a hospital with a specialist haematology unit. Historically, the poor long-term prognosis for many of these patients engendered an attitude of surgical conservatism[3,12]. However, with the increasingly prolonged survival and the improved management of the immunocompromised haematology patient this attitude is clearly no longer tenable.

This paper presents our experience with three cases of neutropenic enterocolitis managed successfully with selective surgical intervention.

Case reports

The haematology department at Auckland Hospital services a population of at least one million. The senior author (J.H.F.S.) provides the surgical consultation for this department and the three cases reported are a true representation of the incidence of neutropenic enterocolitis in the Auckland area. The three cases were seen over a 4-year period.

Case 1

A 13-year-old girl with acute myeloid leukaemia who had completed three courses of chemotherapy (two courses of daunorubicin and cytosine arabinoside and one course of meta amsidyl amsicrine (Park Davis, Auckland, New Zealand) and cytosine arabinoside) was routinely readmitted to hospital 7 days after her last course of chemotherapy. On admission she was well, although thrombocytopenic with a white cell count of $0{\cdot}4 \times 10^9$/litre. Two days later she became febrile (39°C) and complained of abdominal pain. Examination showed no other obvious source of sepsis except for her abdomen, which was diffusely tender with moderate tenderness in the epigastrium. Bowel sounds were present and there were no signs of peritoneal irritation. Blood cultures were taken, which showed no growth after 7 days incubation, and triple antibiotic therapy was commenced with flucloxacillin, gentamicin and metronidazole. The next day the patient's condition had worsened, with a temperature of 40°C and severe abdominal pain, both in the epigastrium and right iliac fossa. There were no signs of peritoneal irritation at this stage. The surgical service was consulted and a presumptive diagnosis of neutropenic enterocolitis was made. A conservative approach was adopted and she was reviewed serially. A supine abdominal X-ray did not demonstrate any abnormality, and stool assay for *Clostridium difficile* toxin later proved to be negative. Within 24 h the patient's condition had deteriorated further, with right sided peritonism becoming prominent, in association with vomiting, diarrhoea and signs of circulatory instability. At laparotomy the serosal surface of the caecum was noted to be mildly congested. No perforation or faecal soiling of the peritoneal cavity was present and a right hemicolectomy with primary ileocolic anastomosis was performed. Histologically this specimen showed mucosal ulceration consistent with neutropenic enterocolitis. Postoperatively the patient had a stormy course with systemic sepsis requiring inotropic support for 4 days. Her blood pressure and vital signs stabilized on the fifth postoperative day, at which time her peripheral blood showed regeneration, with a white cell count of 5×10^9/litre. She made a good recovery and had one further course of chemotherapy without complication before achieving remission.

Case 2

A 14-year-old boy, diagnosed as having acute myeloid leukaemia, was commenced on treatment with cytosine arabinoside and meta amsidyl amsicrine. One month later he was readmitted to hospital with anorexia, fever and abdominal pain localizing to the right iliac fossa. He was commenced on intravenous amikacin, ticarcillin and flucloxacillin. The surgical service was consulted and a diagnosis of probable appendicitis was made. His symptoms settled with the addition of metronidazole to his antibiotic regimen. During the following month he was admitted four times for fever, rigors and abdominal discomfort. Each time these symptoms resolved with parenteral antibiotic therapy consisting of ticarcillin, amikacin and metronidazole. Of the six sets of blood cultures taken during these admissions, one culture plate grew *Staphylococcus aureus* and one grew *Escherichia coli*. An elective appendicectomy was performed 1 month after the patient's initial admission and a good recovery ensued. During this admission a bone marrow biopsy showed a persisting haematological abnormality and he commenced chemotherapy with daunorubicin and cytosine arabinoside. He was readmitted to hospital 14 days after the third course of chemotherapy complaining of fever (39°C) and generalized abdominal pain. Examination showed that he was tender in the right renal angle. The white cell count on admission was $0{\cdot}12 \times 10^9$/litre. Blood cultures were taken (no growth after 7 days

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incubation) and parenteral antibiotic therapy was instituted. During the following 24 h he remained febrile (40°C) and developed signs of peritonism in the right side of the abdomen. Abdominal X-ray showed a lack of psoas shadows bilaterally. Abdominal computerized tomographic scanning showed free fluid, particularly in the right paracolic gutter, but no focal collections. Stool analysis was later positive for *C. difficile* toxin, while urinary microscopy showed no abnormality. An exploratory laparotomy undertaken the following day showed no significant pathology and no surgical resection was undertaken. However, because the patient's condition continued to deteriorate, with gross abdominal pain and signs of sepsis, a further laparotomy was carried out 3 days later. Intraoperatively the caecum appeared normal but a presumptive diagnosis of neutropenic enterocolitis was made and right hemicolectomy was performed, with the formation of an ileostomy and a mucous fistula. Histological examination showed extensive mucosal and submucosal ulceration consistent with neutropenic enterocolitis. Review of the appendiceal histology also showed changes consistent with this diagnosis. Postoperatively the patient made a good recovery with his white cell count returning to the normal range on day 5. Secondary anastomosis was undertaken 3 months later and the patient had remained well with no recurrence of his gastrointestinal symptoms.

Case 3

A 22-year-old man, previously identified as having acute lymphoblastic leukaemia, was admitted 7 days after his last cycle of chemotherapy with cyclophosphamide, vincristine, methotrexate and prednisone. On admission he was febrile (38·5°C) with a white cell count of $0{\cdot}1 \times 10^9$/litre. Physical examination revealed no obvious source of sepsis. Once blood cultures were taken (no growth after 7 days culture) antibiotic therapy was commenced with amikacin, ticarcillin, flucloxacillin and metronidazole. During the following 2 days the patient's condition deteriorated, with continuing fever, generalized abdominal pain and peritonism, and guarding in the right iliac fossa became prominent. The patient vomited once. Bowel sounds were absent and a fullness was palpable in the right iliac fossa by the third day of admission. The surgical service was consulted and a diagnosis of neutropenic enterocolitis was made. The patient was taken to theatre where a gangrenous caecum was found. A right hemicolectomy was performed, with the formation of an ileostomy and a mucous fistula. Histology of this specimen confirmed the clinical diagnosis. Postoperatively the patient made a good recovery. On the tenth postoperative day a collection of straw-coloured fluid (no growth after incubation for 7 days) was drained percutaneously from the supravesical area. Recovery of normal levels of circulating white cells began on the second postoperative day and increased to 5×10^9/litre by the seventh day. The bowel was reanastomosed electively 3 months later with no complication. The patient recovered normal bowel function and suffered no further gastrointestinal upset but unfortunately died following relapse of his leukaemia 5 months after his initial operation.

Discussion

The incidence of neutropenic enterocolitis is unclear. Various investigators have reported incidences between 1 and 46 per cent in patients with leukaemia[4,13,14]. The most comprehensive assessment has been that of Moir and Bale[13] who found that it was a major cause of death in 38 per cent of 50 consecutive autopsies in leukaemic patients. In addition, pathological changes characteristic of neutropenic enterocolitis were present in the gastrointestinal tract of 46 per cent of these patients. In contrast, Amromin and Solomon[4] found evidence of neutropenic enterocolitis in 22 per cent of a series of leukaemic autopsies between 1956 and 1961. Whether this indicates an increase in absolute incidence or simply reflects improved diagnosis and investigation is unclear. However, it does indicate that the disease causes significant morbidity and mortality in patients with leukaemia. Our three cases were collected over a 4-year period, during which time 12 patients with symptoms suggestive of an acute abdomen were seen in the haematology unit. The three cases we have reported were the only patients to require operation; the remaining nine patients settled with non-operative measures. Other investigators have suggested that neutropenic enterocolitis has a spectrum of severity ranging from mild gastrointestinal upset to gross peritonism and systemic sepsis[7,8]. Our experience is consistent with this. It is patients in the latter group who will require surgical intervention.

The aetiology of neutropenic enterocolitis is poorly understood. It characteristically affects the right colon and caecum during periods of profound neutropenia[7–10], particularly in patients with marrow suppression due to a recent course of chemotherapy, typically with cytosine arabinoside[7,8]. The presence of enteric bacteria, particularly the bacillus *Clostridium septicum*, in necrotic areas of the right colonic wall is a consistent finding[9,13,15] and suggests that neutropenic enterocolitis is primarily an infective lesion in an immunocompromised patient. The presence of systemic Gram-negative sepsis in a significant number of these patients is consistent with this hypothesis[7,8]. Various mechanisms of injury to the intestinal mucosa which could aid bacterial invasion have been suggested. These include shock leading to submucosal ischaemia, necrosis of leukaemic infiltrates, bleeding due to a haemorrhagic diathesis[4], abnormal intestinal flora due to aggressive antibiotic therapy[13], and the administration of prednisone[5] or cytotoxics[16]. The relative contribution of these factors to the pathogenesis of neutropenic enterocolitis is unclear, as Geelhoed *et al.*[11] showed that ulcerative caecal lesions may occur in patients with severe neutropenia without any localized predisposing factors.

The characteristic lesion of neutropenic enterocolitis is mucosal ulceration of the caecum and right colon without an accompanying inflammatory response[13]. Other parts of the gastrointestinal tract may be affected but in general these lesions are self limiting[7], while those in the caecum may progress from severe mucosal ulceration to full thickness gangrene. The reasons underlying the increased severity of this disease in the caecum are not clear. Ikard[17] has suggested that, because the colon may have less vascular perfusion than the remainder of the bowel[18,19], particularly during distension[20], and as the caecum is more distensible than the remainder of the colon, submucosal ischaemia can develop within the caecal wall. The impairment in bowel motility seen in inactive and ill patients compounds this problem, leading to mucosal compromise and infection.

The diagnosis of neutropenic enterocolitis remains difficult and a significant number of patients are diagnosed at post mortem[2,7]. As in our three cases, the principal presenting complaints are fever, abdominal pain localizing to the right iliac fossa, vomiting, and watery diarrhoea which may be positive for occult blood. Frank melaena is unusual. Moir *et al.*[7] found that fever was present in all of their 16 patients, as was abdominal pain (this was right sided in seven patients and generalized in nine patients). All but one of these patients had diarrhoea (blood was present in the stool of half of them), while seven vomited or had abdominal distension at some time during their clinical course. Shamberger *et al.*[8] have added the proviso that the presence of these symptoms in the setting of neutropenia (an absolute neutrophil count of less than $1{\cdot}0 \times 10^9$/litre) and cytotoxic therapy should alert the surgeon to the correct diagnosis.

While the symptoms of neutropenic enterocolitis are non-specific, other factors may complicate the diagnosis. Administration of prednisone may mask or ameliorate local symptoms[4], while various cytotoxic agents (e.g. vincristine) are well known causes of abdominal discomfort and gastrointestinal upset[21]. Similarly Sickles *et al.*[22] have reported that physical findings may be minimal in neutropenic patients with severe sepsis.

Our second patient also emphasizes that other causes of the acute abdomen may occur in conjunction with neutropenic enterocolitis. Data from other oncology centres indicate that there is a 5 per cent incidence of acute abdomen in patients with haematological malignancy[6,23,24] and that neutropenic enterocolitis is the cause in under half of them. This patient had his appendix resected 6 weeks before having a hemicolectomy. Revision of the appendiceal histology after the hemicolectomy revealed changes consistent with neutropenic enterocolitis. This patient also had *C. difficile* toxin isolated from his stool although a histological diagnosis of neutropenic enterocolitis was made in the resected colon. The leukaemic patient is at risk of colonization with *C. difficile* due to the aggressive antibiotic policies pursued in these patients[25].

A clinical diagnosis of neutropenic enterocolitis may be suggested by radiological evidence of partial distal small bowel obstruction, thickened and irregular mucosal folds in the caecum, the presence of air in the bowel wall, or a right sided soft tissue mass representing a fluid-filled caecum. Ultrasound and computerized tomographic scanning have also been used to demonstrate a thickened bowel wall[26,27]. Barium enema has been advocated[28], although the danger of perforating a non-viable caecum lends significant risk to this procedure. Geer *et al.*[29] have used peritoneal lavage in diagnosis because this detects significant peritoneal soiling. However, this is only useful in the diagnosis of advanced neutropenic enterocolitis and cannot differentiate between it and other causes of intestinal perforation, such as necrosis of leukaemic infiltrates. Consequently the diagnosis must rest on a high index of suspicion and repeated physical examination, looking for persistence or worsening of abdominal signs[8,30,31].

The management of neutropenic enterocolitis is controversial but a rational approach to treatment can now be formulated. Diagnosis remains the first step in successful management. The fact that this did not occur until after death in a significant number of patients in some studies[6,7] indicates that this remains an area of confusion. There is general agreement that early management should be conservative[7,30]. A standard antibiotic regimen and bowel rest should be commenced. If signs of obstruction are present then nasogastric suction should be commenced. The indications for surgical intervention are less clear. Moir *et al.*[7] and Shaked *et al.*[12] have reported recovery rates of 100 per cent in patients managed without surgical intervention. In contrast, Exelby *et al.*[6] found a mortality rate of 100 per cent in conservatively treated children. However, of the patients treated conservatively by Moir *et al.*[7], one developed a postinflammatory colonic stricture, while two other patients later died of recurrent neutropenic enterocolitis. Thus it is clear that there is a place for conservative treatment but it is associated with significant risks. Our experience is in agreement with that of other centres[7,8,17] in that conservative treatment is warranted initially but the indications for surgical intervention are the same as in an immunocompetent patient, namely: (1) persistent gastrointestinal bleeding after correction of coagulation abnormalities; (2) radiological and/or clinical evidence of imminent intraperitoneal perforation; and (3) general deterioration, or the requirement of large volumes of intravenous fluid or pressor support suggesting uncontrolled sepsis.

The choice of surgical procedure is controversial and to some degree depends on intraoperative findings. Consistently poor results have been reported in patients undergoing appendicectomy or caecostomy for neutropenic enterocolitis[12,30]. Kunkel and Rosenthal[28] have suggested that, in all but very advanced cases, the serosa remains intact despite extensive underlying mucosal damage as these patients are unable to mount an inflammatory response. Thus the poor results obtained with 'minor' surgery may reflect unrecognized extensive disease that was inadequately treated. Case 2 illustrates this point. This patient continued to be symptomatic despite appendicectomy and a caecum which appeared normal at a subsequent laparotomy; hemicolectomy performed at a third laparotomy revealed extensive mucosal disease. The three patients we have reported made good recoveries following standard right hemicolectomy. Histology of all three resected specimens showed extensive disease, although this was not always apparent intraoperatively. Primary ileocolic anastomosis is feasible in the patient without gross peritoneal contamination[7,30,31] as in case 1. However, because the majority of these patients are severely immunocompromised and have significant sepsis, a defunctioning ileostomy with a mucous fistula is an acceptable alternative[7,30,31]. If the stomas are exteriorized close together, the ileostomy can be reversed extraperitoneally once the patient's condition has stabilized, thereby reducing the risk of sepsis. Certainly the complicated postoperative course due to sepsis that occurred in case 1 was avoided in cases 2 and 3. This is particularly notable as case 3 had obvious caecal gangrene at operation. Moir *et al.*[7] have shown that postoperative sepsis is usually the rule in these patients until peripheral neutrophil counts recover. In this respect, granulocyte infusions have been used postoperatively and there is anecdotal evidence that they are beneficial[5,7,23]. Shaked *et al.*[12] have suggested that the return of blood neutrophil levels to normal is the most important determinant of survival and that surgery is unimportant in this regard. While this may be true (and our experience would support it), we believe that the role of surgical intervention in these patients is to remove a localized septic focus, thereby ensuring survival until marrow regeneration occurs. Severe neutropenia is not a contraindication to surgery[24,30,31] and it is clear that untreated peritonitis in the leukaemic patient is uniformly fatal[31].

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Case report

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Subclavian arteritis

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Subclavian arteritis is a rare cause of upper limb ischaemia. It affects large arteries, either unilaterally or bilaterally, although bilateral presentations may not be synchronous. Symptoms are typically shoulder girdle pain, arm 'claudication' or digital ischaemia and diagnosis by arteriography is required. The presentation, clinical findings, investigation and treatment of five patients with subclavian arteritis are analysed.

Patients and methods

A register of patients presenting with a clinical diagnosis of arteritis was kept over 8 years. Of the 104 patients included, five were identified as having subclavian arteritis. They were all women with an age range of 32–70 years (mean 58 years).

Results

The most frequent symptom, affecting four patients, was an aching in the shoulder girdle of the affected side; this was particularly bad at night. Although it bore no relation to movement, it was usually thought to be of musculoskeletal origin. The fifth patient complained of pain on elevation of the arm. Three of the patients developed arm 'claudication', one presented with cyanosis of a cold hand and another with ulceration of the index finger. In two of three patients with bilateral involvement, the presentation was synchronous, but in the third, the syndrome of pain in the shoulder, arm claudication and episodic ischaemia of the hand, recurred in an identical manner on the opposite side 18 months after successful treatment of the first side with steroids. All patients had reduced brachial artery pressure in the affected arm and the distal pulses were reduced or absent. Erythrocyte sedimentation rate measurements in four patients were greater than 40 mm/h in two of them, and one had an unexplained hypochromic anaemia. Delay between the onset of symptoms and diagnosis varied from 3 to 17 weeks, with an average of 9 weeks. Arch and selective arteriography was the most useful diagnostic investigation. Initial treatment with prednisolone, 30–60 mg daily in divided doses, abolished shoulder pain in all patients within 3 days. In three of five patients, arm claudication improved and a skin ulcer healed without further measures. The other two had persistent critical distal ischaemia with rest pain and were treated surgically by subclavian and brachial thrombectomy. Biopsy of the artery was also performed. One of these patients subsequently had a cervical sympathectomy but in no case was surgical bypass required. There were no significant complications and symptoms resolved. Histology of the biopsies showed a panarteritis with intimal thickening and a chronic inflammatory cell infiltrate.

Discussion

Subclavian arteritis is a variety of giant cell arteritis, which was initially thought to involve only the cranial vessels. In a recent review, however, Klein *et al.*[1] found evidence of large peripheral artery involvement in 34 of 248 patients with cranial arteritis, four of whom presented exclusively with claudication of the arm and absent pulses as the initial manifestation of the disease. Classically, giant cell arteritis affects older patients in whom medium-sized muscular arteries are involved, although larger elastic arteries may also be affected. The lesions show intimal thickening, dense chronic inflammatory cell infiltrate, multinucleate giant cells and disruption of the internal elastic lamina[2]. These histological features are identical to those seen in Takayasu's arteritis[3,4], but the latter disease has a distinct geographical and clinical pattern affecting younger oriental women[1,5].

In Takayasu's disease an initial inflammatory phase involves the aorta and largest elastic arteries with a panarteritis. Later medial fibrosis and intimal damage result in stenoses, thromboses, aneurysm formation and dissection. Unlike giant cell arteritis, renal arterial involvement is common, leading to hypertension[1,5], and, in addition, medium-sized muscular arteries (e.g. superficial temporal) are rarely implicated.

The aetiology of subclavian arteritis is unknown. The presentation, histological features and response to treatment could be consistent with an autoimmune lesion, although autoimmune profiles were normal in two of our patients and

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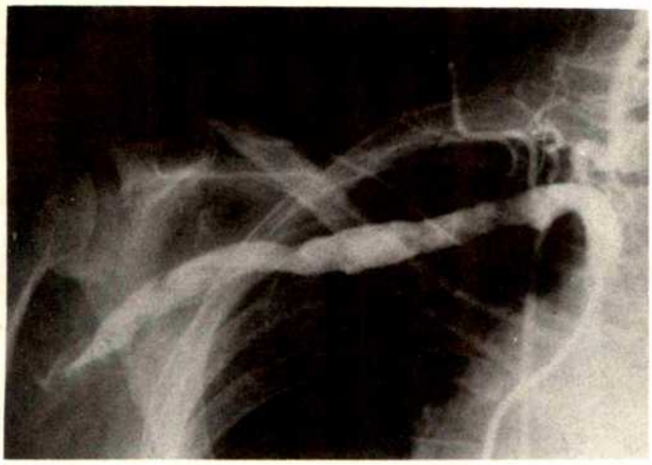

Figure 1 *Arteriography in subclavian arteritis showing segmental ectasia, irregular stenoses and occlusion. Collateral vessels are few in number and of poor calibre*

weakly positive in one. Two of the patients had a previous exposure to tuberculosis and an association with this is possible.

The diagnosis is often delayed. It should be considered in all patients with severe shoulder girdle pain causing sleeplessness, associated with distal ischaemia. Microembolism of the digital vessels requires early diagnosis and treatment as collateralization of occluded digital vessels is poor.

Early arteriography is advised. This demonstrates segmental ectasia and irregular stenoses or occlusions involving the subclavian or axillary arteries. Proximal and distal vessels are of normal size but collateral vessels are of poor calibre and are few in number (*Figure 1*). Intra-arterial clot shows as filling defects. In Takayasu's disease, stenoses, aneurysms and arterial thromboses are evident but, in contrast, collateral vessels are abundant[6]. Gotsman *et al.*[7], discussing selective angiographic features in aortoarteritis, describe a constant feature in subclavian disease with involvement of the vessel beyond the origin of the costocervical trunk as it crosses the first rib. Discrete plaques or intimal ulcers, suggesting focal atherosclerosis, are usually absent in both of the above conditions[1-5].

Initial treatment with steroids in high dosage achieves remission, allowing later reduction to a maintenance dose of 5–15 mg daily. Although a high erythrocyte sedimentation rate is a diagnostic pointer and, if raised, is useful in monitoring response to treatment, a low rate does not preclude the diagnosis. If medical treatment fails, surgical options include thrombectomy, sympathectomy or bypass grafting. In our patients, thrombectomy and sympathectomy were effective in controlling acute limb ischaemia, allowing steroids time to reduce the inflammation. By contrast, Drury and Pollock[8] treated six patients who had subclavian arteriopathy with bypass grafting or excision and interposition grafting of affected areas, with good results. In none of their cases were steroids used and perhaps their use could have avoided the need for surgery.

In our patients, steroids and limited surgery were sufficient to abolish symptoms from 18 months to 5 years. Endarterectomy, which depends for its success on the separation of tissue planes, is not appropriate for these inflammatory lesions, in which the layers of the arterial wall are obliterated by transmural inflammation, but thrombectomy and sympathectomy are helpful where steroids alone are insufficient.

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Abdominal aortic aneurysms: a review of current problems

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This review examines the aetiology and possible methods of prevention of abdominal aortic aneurysm. The natural history of the lesion is discussed. Given its poor prognosis, surgery should be considered even when the patient is over 80 years of age, has stable cardiovascular disease and has a small aneurysm. The case for population screening is reviewed and potential areas of advance in management are outlined.

Keywords: Abdominal aorta, aneurysm, aetiology, screening

Statistics from the Office of Population Censuses and Surveys indicate that one in 70 men who die between the ages of 60 and 84 years do so from a ruptured abdominal aortic aneurysm[1]. It has been pointed out that as the proportion of the population aged over 65 years grows, so we will inevitably be faced with increasing numbers of such cases[2], and indeed there is evidence already of a rising incidence[3–5]. It is known that successful aneurysm repair results in a near normal subsequent life expectancy[6–8], while fewer than one in five survive a rupture[9,10] (less than one in ten in the case of women[5]). This represents an enormous number of potentially preventable premature deaths, given current operative mortality rates of less than 5 per cent in elective cases[11]. Current work in the field centres on attempts to answer four main questions.

1. What is the aetiology of abdominal aortic aneurysm, and is prevention feasible?
2. What is its natural history, and can patient selection be improved in the light of this knowledge?
3. How should screening be carried out, who should be screened and at what cost?
4. Are further medical or surgical advances likely in the near future?

What is the aetiology of abdominal aortic aneurysm and is prevention feasible?

Conventional teaching states that the majority of aortic aneurysms are caused by atherosclerosis, with a very small number due to other specific causes such as arteritis (more common in black populations[12]), tuberculosis and syphilis. However, the sex distribution of the disease, the familial tendency and the proneness of some atherosclerotics to develop stenosing arterial disease while others get aneurysms all imply the presence of another factor or factors besides the mere presence of atherosclerosis. Aneurysm induction in animals on an atherogenic diet has not been productive[13], although animal studies are intrinsically unlikely to be relevant in this field when one considers the surprising difference in medial structure and vasculature between man and most other mammals[14].

That a familial predisposition to aneurysm formation exists seems undeniable. Johansen and Koepsell[15] compared the family histories of 250 patients with aneurysms with those of 250 control subjects. Six of the latter group reported a first degree relative with an aneurysm, while no less than 48 of the former group had such a relative. After adjustment for age and sex, the authors conclude that an increased risk (by a factor of 11·6) attends persons with a first degree relative suffering from an aortic aneurysm. A smaller study from Kentucky[16] describes five patients, each of whom had two or more affected first degree relatives. The possible mechanisms of inheritance have been examined by Tilson and Seashore[17,18]. After looking at the genealogy in families where two or more first degree relatives were affected, they found that in over half the instances the mode of inheritance was consistent with an X-linked dominant gene. However, most of the remainder displayed inheritance from father to son (where the X chromosome of the father is, of course, not transmitted), suggesting an autosomal dominant pattern; nevertheless, the sex ratio in the latter group was still strongly biased towards males. The authors suggest that two distinct forms of the disease may exist: one X-linked and the other inherited as an autosomal dominant gene.

Having postulated an inherited, genetically based deficit we must ask what the physical expression of this defect might be; in other words, what biochemical abnormality is it that exists in these patients? Attention has focused on the activities of three enzyme systems in particular: lysyl oxidase, collagenase and elastase.

Lysyl oxidase is the enzyme which converts lysine residues to aldehydes, a necessary step in the formation of cross-linkages in collagen and elastin molecules. The aneurysm-prone *Blotchy* mouse is known to have defective cross-linkaging owing to low activity of this enzyme, which is linked to the X chromosome[19,20]; the underlying defect is a fault in the copper transport mechanism resulting in low serum levels of copper, an essential cofactor of lysyl oxidase[21]. These facts, along with observations on children with Menkes' syndrome[22] (low serum copper, kinky hair, mental retardation and dilated and tortuous arteries), prompted speculation that low copper levels might be a contributing factor in aortic aneurysm disease.

Tilson has examined copper levels in patients with aneurysms[13]. Post-mortem hepatic copper levels were measured in 13 patients who had died with or from an aortic aneurysm, and were compared with levels in 13 controls with severe non-aneurysmal atherosclerotic disease. The results showed that control subjects had a mean hepatic copper level of almost twice that of aneurysm subjects, although the difference did not attain statistical significance. A subsequent prospective study of eight aneurysm/control pairs of patients measured skin copper levels and again found that levels in aneurysm patients were roughly half those in controls, although, again, statistical significance was not achieved[23]. However, studies by Senapati *et al.*[24] have failed to confirm these findings. In addition, the aneurysms formed by the *Blotchy* mouse do not display the cystic medial necrosis so typical of human aneurysms, occur in the thoracic rather than the abdominal aorta, and are not saccular. Hence, the relevance of copper levels to the aetiology of aortic aneurysms in man is open to doubt but may be important in that subgroup of patients in whom an aneurysm is associated with generalized arteriomegaly[25].

The role of enzymatic proteolysis may be of greater importance in the pathogenesis of the condition. Work in this field dates principally from that of Sumner *et al.*[26], who found that the percentages of collagen and elastin in the walls of

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aneurysmal aortas were significantly lower than those of non-aneurysmal atherosclerotic aortas, even in the outer layers of the wall where there is no laminated clot to act as a diluent to the measured proteins. Collagenase activity has been demonstrated to be appreciably higher in aneurysmal tissue than in non-aneurysmal tissue[27], as has elastase[28] Circulating elastase of leucocyte origin has also been shown to be higher in aneurysm patients who smoke[29]; it is thought that this is due to smoke-induced destruction of α_1-protease inhibitors. However, patients with the Leriche syndrome, who smoked as much as those with aneurysms, showed no changes in elastase activity, perhaps indicating a genetically determined difference in the response to smoking between the two groups. This may be related to the antiprotease status of the patients The principal antiprotease agent *in vivo* is α_1-antitrypsin, normally present in concentrations of 150–400 mg/dl The concentration is genetically determined It is the natural antagonist to elastase, and the relationship between the two is analogous to that between the coagulation and fibrinolytic systems. Abboud *et al.* have shown that heavy-smoking emphysema patients with the PiMZ phenotype, leading to reduced α_1-antitrypsin levels, had significantly greater neutrophil elastase activity[30] It has recently been demonstrated that the elastase:α_1-antitrypsin ratio is significantly increased in patients with aneurysms, especially those suffering rupture[31]. These two lines of research (enzyme system activities in patients with aneurysms and in those with emphysema) have recently been connected by Cronenwett and his colleagues[32]. In a prospective study of 67 patients selected for non-operative management, 30 potential risk factors were measured. The patients were followed for a mean of 36 months and the risk factors were then assessed for their predictive value with regard to aneurysm rupture. Only three factors were independently predictive of rupture diastolic blood pressure, anteroposterior aneurysm diameter and, surprisingly, the degree of obstructive airways disease.

Do these theories concerning the aetiology of aneurysms point to possible preventive measures? Even if the mode of heritability were to be completely worked out, genetic counselling seems of little relevance to a disease which rarely affects people before the age of 60 years, and which is readily treated surgically if detected before rupture occurs. Dietary copper supplements are an attractive idea but probably not of benefit to other than a small subgroup of potential aneurysm formers, which we have currently no way of easily identifying. The only piece of prophylactic advice we can usefully offer at present is one most patients will have heard many times before: to stop smoking

What is the natural history of the disease and can patient selection be improved?

Before surgical repair of aortic aneurysms became established, Estes showed that the 5-year survival rate following diagnosis was only 20 per cent[33]. Even in groups turned down for surgery because of severe intercurrent disease, the cause of death in over a quarter is still rupture of the aneurysm[34,35]. Szilagyi and colleagues demonstrated as long ago as 1966 that the life expectancy after successful repair approached normal[7] and this, together with elective mortality rates of less than 5 per cent in most centres[11], has led to a generally aggressive policy favouring surgery. Reasons commonly put forward for not offering surgery include small aneurysm size, advanced age and medical illness; we would argue that, in many such cases, conservative management is not warranted.

Small aneurysm size is not a justifiable reason for deferring surgery The risk of rupture certainly increases with diameter, as demonstrated by Darling *et al.*[36]. In an autopsy study of 473 patients with unoperated aneurysms, they showed that 60 per cent of aneurysms more than 10 cm in diameter had ruptured, while 45 per cent of those between 7 and 10 cm had done so. However, there was still an appreciable incidence of rupture in the smaller aneurysms a 25 per cent rupture rate in aneurysms between 4 and 7 cm and a 9 5 per cent rate in aneurysms less than 4 cm in diameter. Remembering that there is an 80 per cent overall mortality rate from ruptured aortic aneurysm, this means that approximately one in 12 of unoperated aneurysms less than 4 cm in diameter will cause the death of the patient. Szilagyi *et al.*[34] have also demonstrated that small neurysms are not 'safe' They followed 156 patients with aneurysms of various sizes who had been denied surgery on grounds of unfitness and/or small aneurysm size (which they defined as less than 6 cm) In the 'small' aneurysm group, rupture accounted for 31 per cent of deaths, 39 per cent of these occurring within 2 years of diagnosis Clearly, the figure of 31 per cent would be even higher in a fit population which had been denied surgery on the basis of aneurysm size alone

In Cronenwett's study mentioned above[32], 67 patients with small aneurysms were followed up with serial ultrasound scans for 36 months. The authors confirmed what had previously been reported[37,38]. namely, that small aneurysms increased in transverse diameter by about 5 mm per year, whereas the anteroposterior diameter increased by an average of only 2·2 mm per year. However, the authors found that the initial anteroposterior diameter was a better predictor of eventual rupture than either the transverse diameter or the ratio between the diameters of the aneurysm and the proximal aorta Of the 67 patients, 12 ruptured their aneurysms and eight of these died. Using linear regression techniques, the authors calculate that the presence of a small aneurysm carries a risk of death from rupture of 5 per cent per year Collin[39] has pointed out that, as the death rate from all causes in men aged 60–64 years is 2·2 per cent per year, the presence of a small aneurysm in such a man raises his expected annual death rate by 230 per cent Even in men aged 80–84 years, with a much higher death rate from all causes, the risk of death each year is increased by 38 per cent by the presence of a small aneurysm This seems to us to be strong justification for the elective resection of all small aneurysms, patient fitness permitting.

Mounting evidence also exists that age *per se* is not a reason for withholding surgical treatment. O'Donnell *et al*[40] have reported their experience with 111 octogenarians presenting to their unit with a primary diagnosis of aortic aneurysm over a 15-year period. Thirty patients had ruptured aneurysms and, of these, 23 were operated on Of the 81 patients with non-ruptured aneurysms, 19 had urgent surgery for acute expansion, 44 had elective operations and 18 were not offered surgery on medical grounds (usually severe cardiovascular disease). Thus, the number of patients denied surgery overall was only 25 (22 5 per cent). Of the operated patients with rupture, 74 per cent died, while only 2 per cent (one patient) of those undergoing purely elective surgery died, a rate which, as the authors comment, is comparable to any series of elective aneurysm surgery, irrespective of age. Of the non-operated group, over half had died within 2 years, 59 per cent of the deaths being due to rupture despite the presence of other significant illnesses which had prevented elective surgery. Equally importantly, the authors investigated the quality of life in patients surviving surgery After 1 year, 86 per cent of patients who had undergone elective surgery were judged to be the same as, or better than, before the operation Slightly lower figures were found in the groups having emergency surgery By contrast, less than 40 per cent of non-operated patients had remained as well as before diagnosis, presumably reflecting the progression of their underlying medical conditions.

The authors conclude that most patients aged over 80 years with an aneurysm will do well following elective surgery This is also the conclusion reached by Soreide *et al.*[8], who found a 9 per cent mortality rate attaching to patients undergoing elective aneurysm at the age of 85 years However, details of the selection procedure are not given

Our policy now is to offer elective surgery to all non-obese patients in their eighties who are physically fit and mentally alert, and we would certainly consider surgery in patients even older. General practitioners are perhaps understandably reluctant to refer very old patients with aneurysms[41]; in the light of the disease's natural history and current operative mortality rates, this reluctance would seem to be becoming harder to justify. Certainly, were an 80-year-old man found to have, let us say, a low rectal carcinoma, he would be rapidly referred for consideration of an abdominoperineal resection. Similar urgency should attend the presence of an aneurysm, which has a poor prognosis if untreated but the treatment of which (unlike that of a low rectal carcinoma) is nearly always curative and leads to a good quality of life.

Other factors commonly leading to exclusion from surgery include intercurrent renal, cardiac, malignant and cerebrovascular disease. In a prospective study of 187 patients selected for non-operative treatment, Flanigan *et al.*[42] concluded that current exclusion criteria may be too strict. Although admitting that individual circumstances will, of course, be of prime importance in each case, they specifically recommend that neither stable angina nor a history of myocardial infarction occurring more than 6 months previously should be considered as contraindications to surgery. Similarly, the high level of associated peptic ulcer disease[43,44] should not preclude operation in affected patients; if medical measures fail, a synchronous vagotomy and pyloroplasty has been reported as safe[45].

In summary, the natural prognosis of aortic aneurysm disease is poor. The group of patients to which we should be offering surgery seems likely to expand to include those aged over 80 years, those with stable cardiovascular disease and those with small aneurysms.

Screening: how, who, and at what cost?

If most patients in whom an aneurysm is found fortuitously are offered surgery, it seems logical to look into the feasibility of screening for the disease Simple abdominal palpation is not an adequate method for reliable diagnosis; at least two small-scale screening programmes have confirmed this by comparing ultrasonography findings with physical examination[41,46], while Robicsek has shown that the rates of both false-positive and false-negative results preclude it from consideration as a screening tool[47]. Ultrasound scanning is currently the most practical and accurate way of detecting aneurysms in large numbers of people[48] Most would agree that screening is probably only worthwhile in men, who are affected at least four times more commonly than women[49,50]. Any screening programme will need to be run in conjunction with a vascular surgical unit as many general practitioners will not refer patients with known aneurysms for a surgical opinion[41], although there is evidence that they can be persuaded to do so[51].

If all men in the age group 65–80 years were screened by ultrasound scan, how many aneurysms might one expect to detect? In one of the few pilot studies reported, Collin *et al.* found four aneurysms among 141 men of this age who responded to an invitation to be scanned[52], an incidence of 2·8 per cent, while Scott, scanning 160 people of both sexes in this age group, found an incidence of aortic diameter greater than 3·5 cm of 2 7 per cent[53] Taking into account the operative mortality for elective repair, equipment and staffing costs, the cost of each elective operation performed and the money saved by doing fewer emergency procedures (a ruptured aneurysm costs almost twice as much to treat as an elective one[54]), it has been calculated that each life saved would cost the health service between 6600 and 9000 pounds sterling[55,56]. Both these figures are substantially less than the 15 000 pounds sterling, 'or very likely much more'[57], that it would cost to save a life by mammographic breast cancer screening

If this is considered too expensive, it might be possible to screen high-risk groups Males with hypertension or with peripheral vascular disease are two subgroups which have been the subject of pilot studies. Two studies of men with peripheral vascular disease revealed incidences of aortic aneurysm of 12 per cent[58] and 9·6 per cent[59]. Incidences of 10·7 per cent[60] and 5·3 per cent[49] have been reported in elderly male hypertensives, although a larger Swedish study found only one aneurysm in 245 patients attending a hypertension clinic[61]. In this study, however, both sexes were included, and the upper age limit was set at 70 years, which was perhaps too young for the purpose.

Two other groups worth screening would seem to be first degree relatives of known aneurysm patients[15] and patients with chronic obstructive airways disease. The latter are not known to have a higher incidence of aneurysms, but when they do get one it appears to carry a higher risk of rupture[32].

Are further surgical or medical advances likely in management?

The refinement of surgical techniques in abdominal aortic aneurysm repair has been reviewed by Bergan[62], and further simplification seems unlikely at present. The use of the external pneumatic counter-pressure G-suit (J. C. Peacock and Son Ltd., Newcastle upon Tyne, UK), introduced in the early 1970s as a method of controlling intra-abdominal haemorrhage pre-operatively[63], has not become widespread. The ringed intraluminal graft, involving sutureless anastomoses, may find a role in the management of ruptured aneurysms, especially in the obese and those with very friable aortas[64]. Much of the reduction in mortality rates in recent years is because of improved anaesthesia and (in the case of rupture) resuscitation. Autotransfusion is fast becoming an accepted technique in all branches of surgery involving major blood loss and has been successfully used in aneurysm repair[65]. Its use may be life saving when antibodies cause difficulties with the rapid cross-matching of blood. Further reduction in death rates seems likely to come from increasing the ratio of elective to emergency operations, and this is the desired effect of any screening programme.

Some intriguing work on the correction of low α_1-antitrypsin levels may be relevant to the future medical management of abdominal aortic aneurysms. Wewers *et al.* have found that α_1-antitrypsin levels can be significantly increased in deficient patients by the administration of danazol[66] and to a lesser extent by tamoxifen[67]. These agents act by stimulating the hepatic synthesis and release of α_1-antitrypsin. Although this work was done with the treatment of panacinar emphysema in mind, it raises the concept of reducing the risk of aneurysm rupture by lowering the elastase:α_1-antitrypsin ratio, the balance of which seems to be altered in many aneurysm patients.

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Relationship between DNA ploidy and survival in patients with primary breast cancer

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The DNA ploidy of breast cancer tissue from paraffin blocks was measured by flow cytometry in 117 patients whose disease had been detected and treated with surgery between 1974 and 1976. Patients with aneuploid tumours had positive axillary nodes and distant metastases more often than those with diploid tumours. Aneuploid tumours were more common in postmenopausal than premenopausal women. The S-phase fraction (SPF) was significantly higher in aneuploid than in diploid tumours and positive axillary lymph nodes were found in 26 per cent of the patients who had a tumour with a SPF below the median (4·8 per cent) and in 48 per cent of those with tumours with SPF values above the median. At the primary clinical investigation 2 per cent of the patients with diploid tumours and 6 per cent of those with aneuploid tumours had distant metastases. During the follow-up, the proportion of patients with distant metastases increased to 42 and 72 per cent, respectively. With a follow-up of 11·5 years, the DNA aneuploidy of the tumour showed a significant association with decreased survival. Thirty-three per cent of patients with diploid and 65 per cent of patients with aneuploid tumours had died from breast cancer during the follow-up ($P<0{\cdot}001$). All patients with hypertetraploid or multiploid tumours died from breast cancer. High SPF values were associated more closely with distant metastases or death during the follow-up than low SPF values. Our results suggest that DNA ploidy measured by flow cytometry from paraffin embedded tissue blocks of human breast cancer can be used to predict the aggressiveness of the tumour and the survival of the patients.

Keywords: Breast cancer, tumour ploidy, survival

Previous reports based on microspectrophotometric measurements of DNA have suggested that the ploidy of the cells in neoplastic tissue from patients with primary breast cancer may be of prognostic value[1,2]. In earlier studies with flow cytometry the association of DNA content with prognosis, remission time, disease free survival, and lymph node involvement has been demonstrated, but the results are not uniform[3–5].

We have undertaken a study to measure the DNA content of paraffin embedded primary breast cancer tissue by flow cytometry, because most of the flow studies have been done with fresh material and the follow-up time has been short. Our series consists of breast cancer patients treated initially by surgery alone from 1974 to 1976 at the Kuopio University Central Hospital.

The aim of this study was to investigate the relationship between tumour ploidy and prospectively recorded prognostic factors in a group of patients whose clinical history was already known. We wanted to study especially the relationship between DNA ploidy and survival in patients with primary breast cancer.

Patients and methods

The original material consisted of 119 women with primary breast cancer treated mainly under the care of one surgeon (P.P.) at the Surgical Department of University Central Hospital of Kuopio, Finland. In two cases the flow cytometry investigation was unsatisfactory and these patients were excluded. Of the remaining patients, 55 had been subjected to a modified radical mastectomy (Patey)[6] in which the major pectoral muscle was preserved but the pectoralis minor muscle removed. Nine patients had been subjected to a modified radical mastectomy in which the pectoral muscles were saved, but the muscle fascias stripped. Simple mastectomy had been performed in 53 patients. All methods included axillary node evacuation. None of the patients received chemotherapy preoperatively. Postoperative radiotherapy was given if the tumour was stage II or a higher stage[7]. For all these patients a series of prognostic factors had been recorded at mastectomy, including the age of the patient, menopausal status, lymph node status, tumour size, presence of distant metastases, and histological classification. The mean follow-up time was 12·4 years (range 11·5–13·3 years).

Patients were classified as premenopausal if they were still menstruating at the time of surgery and under the age of 52 years. Lymph node staging was done at the time of mastectomy using axillary node and fat evacuation, and the node involvement was judged histologically. All lymph nodes were serially sliced to sections which were 4–5 mm thick, embedded in paraffin, sectioned at 5 μm, stained with haematoxylin and eosin, and examined by microscopy for micrometastases. Tumour size was recorded as the maximum diameter measured in the fresh mastectomy specimen. Metastatic lesions were detected by bone and liver radio isotope scan, liver ultrasound, routine laboratory tests reflecting the bone and liver metabolism, and bone and chest radiography. Metastases were verified by surgical biopsy, when possible. Patients with metastases were given hormonal therapy if the tumours were receptor positive.

All patients were followed up in the outpatient department by the same surgeon. In the first 12 months, they were examined every 3 months, then at 6-monthly intervals for 72 months, and annually thereafter. Survival and the time elapsed before recurrence were recorded.

Samples for DNA determination were prepared from paraffin blocks using a modification of the method described by Hedley[8]. Blocks with representative tumour tissue were chosen. From these, two 50-μm-thick sections were cut and deparaffinized. Better nuclear samples are obtained by using 50-μm-thick sections[9] than 30-μm-sections as originally described by Hedley[8]. The pepsin treatment of the deparaffinized sections was replaced by proteinase K (Sigma Chemical Company Ltd., Poole, UK) treatment (30 min at 10 μg/ml) at room temperature, which in our hands gave somewhat improved results. After filtration the nuclei

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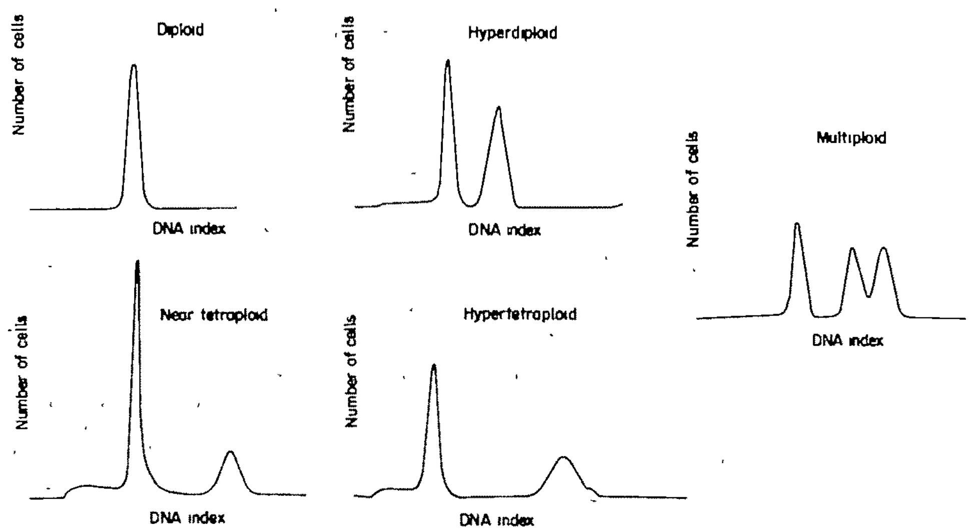

Figure 1 *Typical peak patterns of breast carcinoma with various ploidy, the peak with the lowest ploidy value was considered to be diploid*

Table 1 *DNA ploidy distribution, frequency of axillary lymph node involvement and frequency of distant metastases present at the time of primary investigation and during the follow-up period, 11·5–13·3 years*

DNA ploidy type (DNA index)	Number of patients	Number of patients N	Ma	Mb
Diploid (1·00–1·049)	45 (38)	13 (29)	1 (2)	19 (42)
Hyperdiploid (1·05–1·75)	31 (27)	17 (55)	1 (3)	20 (64)
Near tetraploid (1·76–2·00)	16 (14)	6 (38)	1 (6)	11 (69)
Hypertetraploid (>2·00)	5 (4)	3 (60)	1 (20)	5 (100)
Multiploid	20 (17)	9 (45)	1 (5)	16 (80)
Total	117 (100)	48 (41)	5 (4)	71 (61)

Figures in parentheses are percentages; N, axillary lymph node involvement, Ma, frequency of distant metastases at time of primary investigation; Mb frequency of distant metastases during follow-up

were treated with 10 μg/ml RNAase and stained with 25 μg/ml ethidium bromide (Sigma Chemical Company Ltd.) for at least 1 h. The DNA was determined by flow cytometry with a FACS IV (Becton Dickinson UK Ltd., Oxford, UK) instrument using the emission at 488 nm at 200 mW. The total emission above 560 nm was recorded. Samples with a coefficient of variation above 8 per cent were rejected. There were two such cases out of 119 in our basic material. As the staining intensity of fixed nuclei varied from one sample to another, no internal standard was included. The lowest peak was given a DNA index value of 1 and the DNA indices of other peaks were calculated with this as a reference. Thus there were no hypodiploid tumours in our material. The S-phase was calculated using the built-in computer program in the FACS IV. Tumours with a DNA index of 1·00–1·049 were recorded as diploid, those with a DNA index of 1·05–1·75 as hyperdiploid, and those with a DNA index of 1·76–2·00 as near tetraploid. The cut off point, 1·75, between these two categories is somewhat low but is based on our experience on the location of the G2 population using our methodology. Tumours with a DNA index >2·0 were considered hypertetraploid. The grouping of cases is shown in *Table 1* and typical peak patterns in *Figure 1*. In this paper we defined aneuploid tumours as tumours with a DNA index outside the diploid range. This definition also includes multiploid tumours.

Statistical analysis was performed at the University of Kuopio using the SPSS-X (SPSS Incorporated, USA) program in a VAX 11/780 (Digital Equipment Corporation, USA) computer. Differences between the groups were analysed by the χ^2 test and *t*-test. Actuarial survival curves were calculated according to the life-table method. Survival was calculated by counting as breast cancer deaths only patients who died with known metastases and censoring for non-cancer deaths. Survival without censoring for non-cancer deaths is referred to as 'crude survival'.

Table 2 *DNA ploidy, age, and menopausal status in 117 patients with breast carcinomas*

DNA ploidy	Mean(s.d.) age (years)	Premenopausal	Postmenopausal	Total
Diploid	55·7 (14·6)	21	24	45
Aneuploid*	60·3 (12·1)	17	55†	72

*Includes hyperdiploid, tetraploid, hypertetraploid, and multiploid tumours; †$P=0·05$ (difference between premenopausal and postmenopausal women)

Results

Of the breast cancers analysed, 45 of 117 (38 per cent) had a diploid DNA index, the remaining 72 tumours (62 per cent) were aneuploid (*Table 1* and *Figure 1*). The diploid tumours were detected in younger patients (mean(s.d.) age 55·7(14·6) years) than the aneuploid tumours (60·3(12·1) years) but the difference was not statistically significant ($P=0·10$). The near tetraploid and hypertetraploid tumours occurred in still older patients (mean (s.d.) age 63·0(12·8) years and 68·1(7·5) years respectively, *Table 2*; $P=0·10$). Of the 117 patients 38 (32 per cent) were premenopausal. The premenopausal patients had about the same number of diploid and aneuploid tumours, but more than twice as many of the postmenopausal patients had aneuploid tumours than had diploid ones. The difference is statistically significant ($P \leqslant 0·05$; *Table 2*).

There was no statistical difference in the size of diploid (mean(s.d.) diameter 3·3(2·3) cm) and aneuploid tumours (3·5(1·8) cm, $P=0·65$).

Lymph node involvement was observed at the time of primary investigation in less than one-third of the patients with diploid tumours (*Table 1*) and in about half of the patients with aneuploid tumours. The difference is statistically significant ($P \leqslant 0·05$). At the time of primary investigation only one patient with a diploid tumour and four patients with aneuploid tumours had distant metastases. During the follow-up there was a substantial incidence of metastases, so that at the end of the study 42 per cent of the patients with diploid tumours, and 72 per cent of the patients with aneuploid tumours had distant metastases (*Table 1*). The difference is statistically highly significant ($P<0·001$). One-third of the patients with diploid cancer and two-thirds of the patients with aneuploid tumours died of their disease (*Table 3*). The difference is statistically highly significant ($P<0·001$).

The S-phase fraction (SPF) of the tumour cells could be determined in 54 cases. The SPF was significantly higher in aneuploid than in diploid cancers. The median of SPF in our material was 4·8 per cent. The means(s.d.) were: diploid tumours 5·9(4·0) per cent; aneuploid tumours 8·3(7·3) per cent. However, the difference is statistically not significant. Tumours

Table 3 *Deaths of the breast cancer patients with tumours of different ploidy*

DNA index	All patients	All deaths	Breast cancer deaths
Diploid (1·00–1·049)	45	24	15
Hyperdiploid (1·05–1·75)	31	22	20
Near tetraploid (1·76–2·00)	16	11	9
Hypertetraploid (>2·00)	5	5	5
Multiploid	20	13	13

Table 4 *Tumour size, frequency of axillary lymph node involvement at the time of primary investigation, distant metastases during the follow up, the number of patients who died of breast cancer and the number who died of any cause during the follow-up period*

Parameter	SPF<median	SPF>median	*P* value*
Tumour size (cm)	2·7	3·8	0·05*
Nodes at primary investigation	7/27	13/27	0·09†
Metastases during follow-up	10/27	18/27	0·04†
Breast cancer deaths	8/27	14/27	0·10†
All deaths	14/27	18/27	0·27†

SPF, S-phase fraction; * Student's *t* test; † χ^2 test

Table 5 *Tumour size, frequency of axillary lymph node involvement at the time of primary investigation, distant metastases during the follow-up, the number of patients who died of breast cancer, and the number who died of any cause during the follow-up*

Parameter	SPF<7·0%	SPF>7·0%	*P* value*
Tumour size (cm)	2·9	4·0	0·08*
Nodes at primary investigation	10/35	13/19	0·08†
Metastases during follow-up	14/35	15/19	0·02†
Breast cancer deaths	9/35	13/19	0·0023†
All deaths	17/35	15/19	0·0300†

SPF, S-phase fraction; * Student's *t* test; † χ^2 test

below the median SPF ($n=27$) were smaller (mean diameter 2·7 cm) than tumours above the median SPF ($n=27$; 3·8 cm). The difference is statistically significant ($P=0·05$). A quarter of the patients with tumours where the SPF was below the median and half of those with tumours where the SPF was above the median had lymph node metastases, but the difference was not significant (*Table 4*). As regards distant metastases, there was a correlation with the SPF (*Table 4*), but no difference could be detected in relation to deaths. When 7·0 per cent, rather than the median 4·8 per cent was chosen as the cut off point for SPF, the difference between the groups increased (*Table 5*)

The difference in the 11·5 year survival was statistically significant between patients with diploid and aneuploid tumours when tested by life-table analysis (*Figures 2* and *4*). When 7·0 per cent was chosen as the cut off point for the SPF, the difference between the groups increased considerably (*Figures 3* and *5*). There was little difference between tumours with a SPF of 3·5–7·0 per cent and those with a SPF <3·5 per cent (*Figures 3* and *5*). This was true both for the survival (breast cancer deaths only; *Figure 3*) and for the crude survival (all deaths; *Figure 5*).

Discussion

Flow cytometric DNA analysis is a rapid, objective, and reproducible method for the routine examination of fresh tissue and also of fixed paraffin embedded tissue[10]. In a retrospective study fresh tissue is not available, but paraffin blocks are readily available. In our study such samples were suitable for DNA ploidy analysis, and only two of 119 tumours (2 per cent) had to

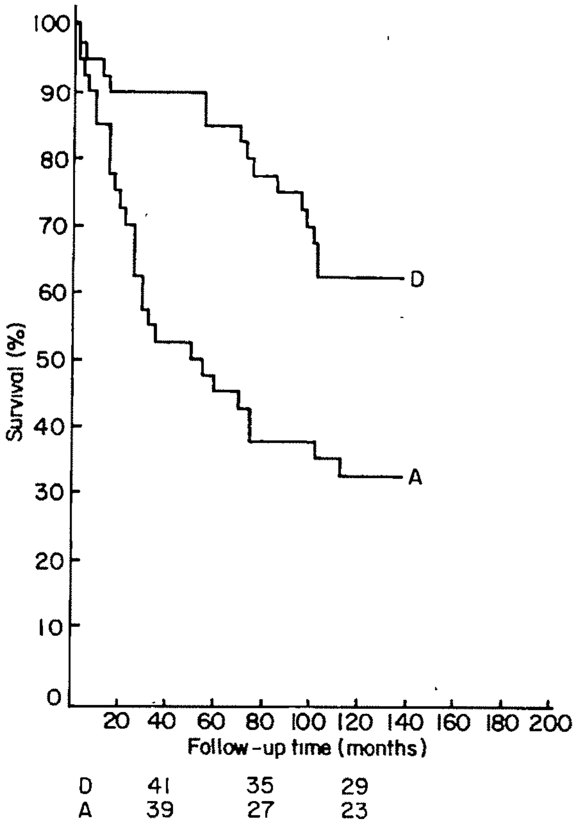

Figure 2 *The survival of patients in the diploid (D) and aneuploid (A) groups The analysis was based on breast cancer deaths only;* $\chi^2=14·99$, $P<0·001$

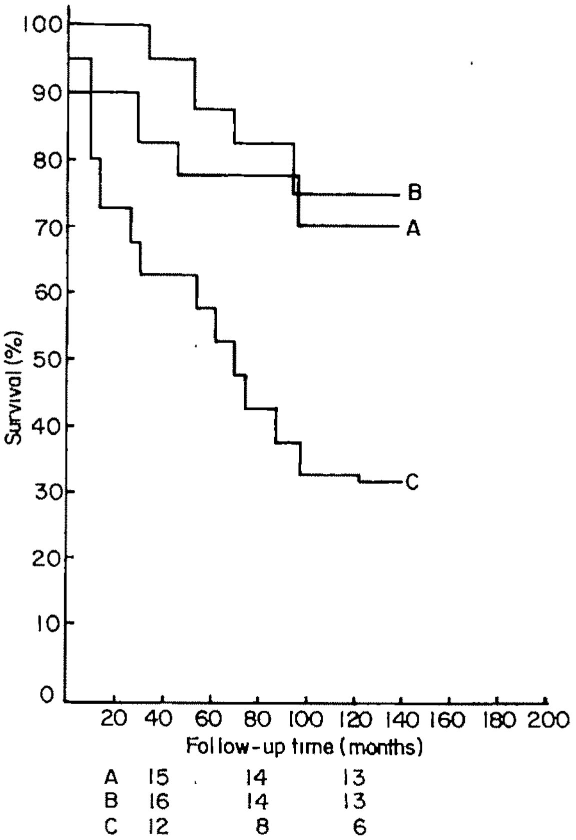

Figure 3 *The survival of patients in groups with different S-phase fractions (only breast cancer deaths included in the analysis): A, SPF<3·5 per cent* (n=18), *B, SPF=3·5–7·0 per cent* (n=17), *C, SPF>7·0 per cent* (n=19), $\chi^2=9·239$, $P=0·0099$

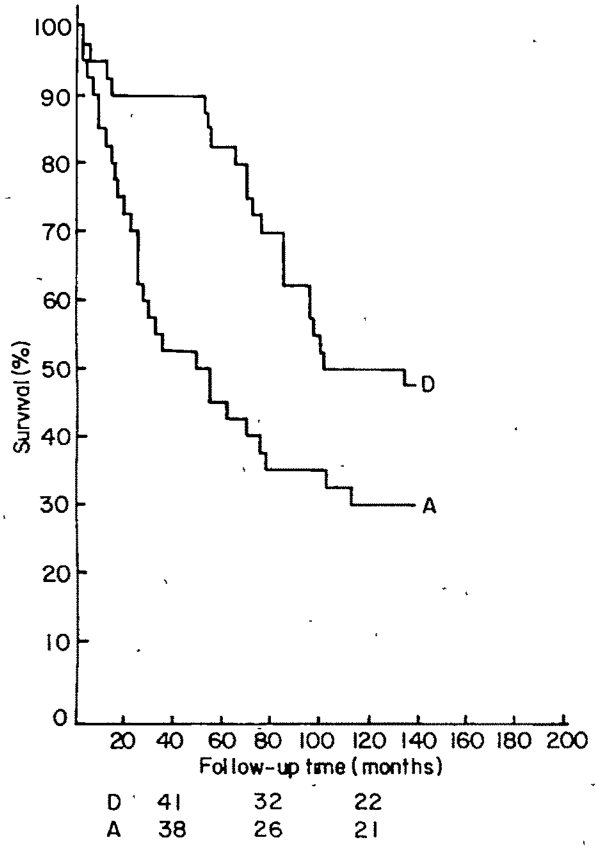

Figure 4 *Crude survival of patients with diploid (D) and aneuploid (A) tumours*, $\chi^2 = 11{\cdot}13$, P<0·001

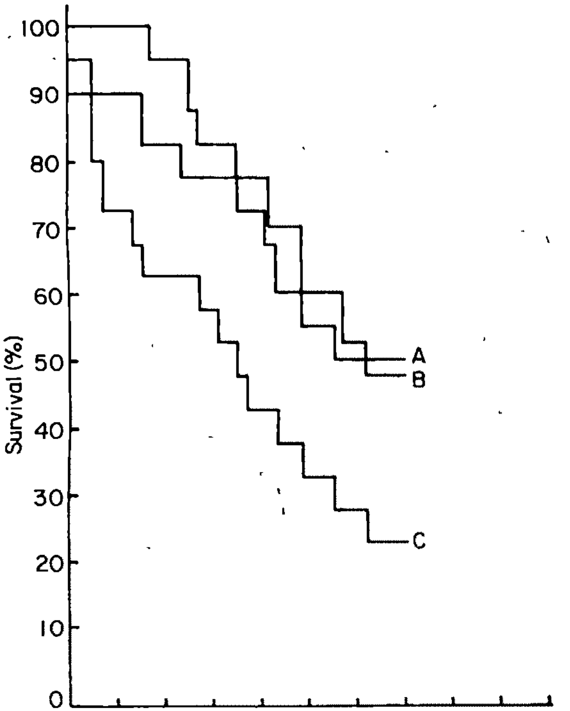

Figure 5 *Crude survival of patients in groups of different S-phase fractions*: *A*, *SPF*<3·5 *per cent* (n=18), *B*, *SPF*=3·5–7·0 *per cent* (n=17), *C*, *SPF*>7·0 *per cent* (n=19) $\chi^2 = 6{\cdot}244$, P=0·0441

be rejected because of poor technical results. It seems that flow cytometry offers a good basis for the development of a diagnostic grading system[11]. Our study was designed to clarify some of the discrepancies which have emerged in studies on DNA flow cytometry of breast cancer, and to explore the potential uses of this method in diagnostic and prognostic grading

Our material was collected, diagnosed, treated and followed up mainly by one surgeon, and therefore the diagnostic criteria and therapeutic decisions are as uniform as possible This eliminates interobserver and interlaboratory variations[12,13], which may greatly decrease the power of an analysis of biological and clinical correlations.

In our material there was a difference in survival between breast cancer patients with diploid and aneuploid tumours after a mean follow-up of 12·4 years. Previously aneuploidy has been reported to correlate with a poor survival[3,4,14] after a follow-up of 2·8–7·7 years. However, another study, where the follow-up time was 7·7 years, failed to show a difference in survival between diploid and aneuploid tumours[5]. Our present results support the former findings. Our follow-up time seems to be one of the longest reported in the literature.

Published reports give conflicting results about the correlation between tumour size and tumour ploidy Some reports like our present one fail to show a statistically significant difference[14–16]. Though in many of these studies the aneuploid tumours have been somewhat bigger. In those studies where a significant difference has been found the aneuploid tumours have always been bigger than diploid ones[4,5,17]. The larger size of the tumour correlates with the age of the tumour and its growth rate. Direct measurements of tumour doubling time in human breast cancer cannot easily be done and requires fresh tissue. An estimate can be made by studying the mitotic rate by normal light microscopy[18,19] or the SPF by flow cytometry. Both of these methods give results which correlate with patient survival. In our study, tumours with SPF below the median were smaller than those above the median. On average, the proliferation rate in small tumours (usually diploid) is lower than in large tumours (usually aneuploid).

Aneuploid tumours showed a statistically significant association with the presence of axillary lymph node metastases Earlier studies have failed to demonstrate such an association[5,14–16], but again, even though statistically significant differences have not been detected, aneuploid tumours have generally been associated with a higher number of cases with positive axillary lymph nodes. In the present study aneuploid tumours showed a significant association with distant metastases. Earlier reports have been conflicting[5,14,15]. In the present study distant metastases were more common in patients with aneuploid tumours at the time of primary surgery, and during the follow-up, patients with aneuploid tumours developed distant metastases more often than those with diploid tumours.

Breast cancer patients with tumours below the median SPF value had significantly fewer distant metastases than those with tumours above the median. Kallioniemi *et al.*[15] also found this association. The finding suggests that activated cell kinetics and distant metastases are associated. Baak *et al.*[18] have demonstrated that the mitotic activity index is the most prominent prognostic parameter in the histology of breast carcinoma. Our Finnish study[19] also showed that mitotic activity index is important, although not to the same extent as in the study from The Netherlands[18]. Mitotic index and SPF do not measure the same parameters. The mitotic index varies in different parts of the tumour and is therefore measured where the mitotic activity is highest, at the periphery. In flow cytometry no distinction is usually made between the centre and periphery of the tumour. Because of this, there is a considerable sampling variation, which may affect the results. It has been shown that when multiple samples are taken from the same tumour there is some variation in the DNA index and a much greater variation in the SPF[20]. The biological importance of the SPF is demonstrated by the fact that there is a statistically significant difference in survival between patients with a SPF above and below 7·0 per cent.

Acknowledgements

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Clinical, radiological and cytological diagnosis of breast cancer in young women

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In women over the age of 35 years, an accurate diagnosis of breast cancer can be made in over 95 per cent of patients using a 'triple assessment' system collating information from clinical examination, mammography, sonomammography, and fine-needle aspiration cytology. These methods have not been specifically evaluated in women aged 35 years or less, hence a study was undertaken on 30 such patients. Clinical examination was unreliable in predicting malignancy with a sensitivity of only 37 per cent. Thirty per cent of patients presented with a lump which had the clinical features of a fibroadenoma. Radiological methods were less sensitive in detecting malignancy in this age group than in older patients. The sensitivity of aspiration cytology was 78 per cent which was higher than that for breast cancer at all ages. Histology showed that there were fewer low grade tumours and fewer scirrhous tumours in this age group than in a control group of women aged over 35 years. This study indicates that cytological confirmation of apparently benign focal breast lesions in young women is essential, especially when these are managed conservatively.

Keywords: Breast cancer, cytology

The diagnosis of breast cancer in young women is unexpected and alarming to both patient and clinician. In women over the age of 35 years an accurate diagnosis of malignancy without histology can be made in over 95 per cent using a 'triple assessment' system collating information from clinical examination, X-ray mammography and aspiration cytology[1-4]. If ultrasound mammography is added the diagnostic sensitivity is further enhanced[5]. These methods have not been specifically evaluated in women aged 35 years or less. It is in this age group that the nature of palpable breast lesions must be established if apparently benign lumps, particularly fibroadenomas, are to be managed conservatively as recently advocated[6,7].

A study was undertaken to assess the diagnostic sensitivity of clinical examination, X-ray mammography, ultrasound mammography, and aspiration cytology, used alone and in combination, in women between 19 and 35 years of age with primary breast cancer.

Patients and methods

All patients under 36 years of age who presented to the Southampton Breast Clinic with a palpable mass between January 1980 and March 1988 and who were found to have breast cancer were studied and analysed retrospectively

All patients were investigated by clinical examination and the majority had X-ray mammography, ultrasound mammography, and aspiration cytology. Each modality was assessed on a five-point scale, previously developed in Southampton[4] (−2, definitely benign; −1, probably benign; 0, inconclusive, +1, probably malignant; +2, definitely malignant) and an overall score obtained. Patients with scores between −6 and −1 were treated by excision biopsy, scores between 0 and +3 required Trucut® biopsy (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) or occasionally frozen section, and scores between +4 and +6 were treated by definitive surgery provided cytology had a positive score.

Histology was available on all pateints. A control group of 30 consecutive patients aged over 35 years was taken from women with operable carcinomas attending the breast unit during the same time period. Bloom's grading was ascribed to each tumour as was the degree of fibrous stroma (see below).

The scoring system allows an objective comparison of the diagnostic sensitivity of each method in detecting malignancy Each patient was examined in the breast clinic by either a consultant or a senior registrar A Phillips 7100 Static B® scanner (Phillips, Eindhoven, The Netherlands) was used for the ultrasound examination; a 7 5 MHz transducer was applied directly to the skin, scanning at 2-mm intervals over the breast mass The investigation was performed and interpreted by one of two radiologists with an interest in breast disease X-ray mammography was performed using a Senograph® (CGR Senographic, Paris, France) X-ray set with Kodak Min-R® (Hemel Hempstead, UK) film, standard craniocaudal and lateral oblique views were taken

Aspiration cytology was performed with a 21 gauge needle and disposable syringe mounted on a syringe holder. Suction was applied as the needle was introduced into the lesion several times The contents of the syringe were then expressed on to slides, half of which were immediately air dried and the remainder fixed in acid-alcohol

Results

There were 30 patients (median age 31 years. range 19–35 years); the duration of symptoms was from 3 weeks to 6 months, with a mean of 9 weeks. One patient was pregnant and two were lactating.

Eighteen patients presented with a painless lump, in ten the lump was painful, and in two pain was the only presenting feature, although at examination a lump was palpable. Eleven lumps (37 per cent) were clinically malignant (scores +1 or +2) and six lumps were of indeterminate nature (zero score), giving a total of 57 per cent with some suspicion of malignancy. Thirteen (43 per cent) were considered benign (nine clinical fibroadenoma, four benign breast change).

X-ray mammography was performed on 22 patients (*Table 1*), this showed evidence of malignancy (+1 or +2 scores) in 12 (55 per cent), and was indeterminate (0 score), mainly due to breast density, in five, together giving an X-ray suspicion of malignancy in 77 per cent. A benign diagnosis was made in five (23 per cent) due to well-defined masses in four patients, and severe glandular density obscuring one tumour.

Twenty-six patients underwent sonomammography This showed evidence of malignancy in 15 (58 per cent) and was inconclusive in a further three tumours, resulting in a suspicion of malignancy in 69 per cent. Eight tumours were diagnosed benign initially (six fibroadenoma, two fibrocystic change),

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Table 1 *Total of 30 proven malignancies. distribution of scores for each method of assessment, sensitivities for malignancy and number of false negatives*

	Clinical examination (*n*=30)	X-ray mammography (*n*=22)	Ultrasound mammography (*n*=26)	Final cytology (*n*=27)
Score				
−2	9	—	—	—
−1	4	5	8	1
0	6	5	3	4
+1	8	9	9	5
+2	3	3	6	16
Unsatisfactory	—	—	—	1
Sensitivity. score +1 or +2 (%)	37 (14–48)	55 (32–76)	58 (37–77)	78 (58–91)
Sensitivity score 0, +1 or +2 (%)	57 (27–64)	77 (55–92)	69 (48–86)	93 (76–99)
False negative. score −1 or −2 (%)	43 (36–73)	23 (8–45)	31 (14–52)	4 (1–24)

Values in parentheses are 95 per cent confidence intervals

when reviewed retrospectively the impression was changed in five to indicate malignancy; three of these occurred during the very early experience of breast ultrasound.

As described in previous papers[4,8–10] the scoring system for cytology defines an obvious malignant aspiration as +2, reserving +1 for well differentiated carcinomas and poorly cellular malignant aspirates. Zero scores are equivocal and therefore suspicious of malignancy; +2 and +1 scores are regarded as positive. Cytology showed malignancy in 21 of 27 patients (78 per cent), it was equivocal in four other patients, increasing the suspicion of malignancy to 93 per cent. There were two false negative results. In addition there were three cellular aspirates which when repeated proved positive in one and equivocal in one.

As the investigations were added to the clinical diagnosis, sensitivity for carcinoma rose from 54 per cent for those undergoing clinical examination and sonomammography to 71 per cent for those undergoing clinical and X-ray examination; when these three procedures were combined, the sensitivity was 75 per cent for carcinoma. Clinical examination with fine-needle aspiration gave a 90 per cent sensitivity, and, when imaging was added to these, 95 per cent of all cancers were recognized preoperatively. In two patients, malignancy was not positively identified by any method (neither had X-ray mammography, however); in both cases the lesion was thought to be a discrete area of benign breast change. The lesions in the two patients who did not have aspiration cytology were clinically and radiologically considered to be fibroadenoma (*Table 1*).

Aspiration cytology correctly identified six cases as malignant, when other modalities gave inconclusive or benign results. Similarly, three carcinomas were correctly identified by X-ray mammography and by ultrasound when aspiration cytology was inconclusive.

Most of the carcinomas were ductal in origin (*Table 2*). Four of these were predominantly *in situ* and one was entirely *in situ*. These five could not be ascribed a Bloom's grade.

Twenty-five invasive carcinomas were compared with a control group of 30 carcinomas from women aged over 35 years by ascribing a Bloom's grade to the tumours and assessing the degree of fibrous stroma on a three-point score. The two groups were combined and read 'blind' on two occasions by one observer (A.H.). The two readings gave 87 per cent correlation, where the observations disagreed, a third deciding reading was made which in most instances agreed with the second reading. There was a significantly smaller proportion of low grade (Bloom's grade I) and densely scirrhous tumours in the carcinomas in young women than in controls (*Table 3*).

Table 2 *Histopathological subtypes*

	n
Invasive ductal carcinoma	13
Invasive ductal with ductal *in situ*	12*
Invasive ductal with lobular and ductal *in situ*	1
Intraductal carcinoma, without invasion	1
Lobular invasive carcinoma	1
Medullary carcinoma	2

* Including four predominantly ductal *in situ* with focal invasion

Discussion

Breast cancer in women below the age of 35 years is uncommon, and a diagnosis needs a high index of suspicion, as shown by the delay in reaching a diagnosis in some of these patients; a similar observation has been recorded previously[6].

The value of combined clinical examination, imaging and fine-needle aspiration cytology in breast cancer diagnosis is well established[1–5]. However, these studies have largely been conducted with women over 35 years of age in whom each method has a high sensitivity for malignancy and, when used in conjunction, provide an accurate preoperative diagnosis in up to 99 per cent of patients with breast cancer[5].

In women aged under 35 years, clinical examination, mammography and ultrasound were less accurate than in older patients. Clinical examination diagnosed cancer in only 11 (37 per cent) patients and was suspicious in a further six (total 57 per cent), compared with the 85 per cent total sensitivity in older patients. Nine patients (30 per cent) presented with a lump which had the clinical features of a fibroadenoma (i.e. small, discrete, solid and mobile). X-ray mammography showed an overall sensitivity of 77 per cent compared with 93 per cent recorded previously in older patients; this is attributable to greater breast density in younger patients and to good border definition of some cancers. Sonomammography indicated carcinoma in only 69 per cent, although it identified lesions in

Table 3 *Bloom's grade and fibrous stroma compared in women aged 35 years or less and women over 35 years*

	Bloom's grade				Fibrous stroma			
	I	II	III	Total	+	++	+++	Total
Women 35 years or less	2	11	12	25	7	17	1	25
Controls (over 35 years)	16	7	7	30	4	17	9	30
Total	18	18	19	55	11	34	10	55

the other patients, labelling them benign. Five of these eight false negative results occurred in the early stages following the introduction of breast ultrasound[11]; when reviewed, greater experience identified malignant features in three, which would have increased the sensitivity (positive and suspicious lesions) to 80 per cent However, in our hands the sensitivity of ultrasound for carcinoma is now of the order of 93 per cent, but there remains an overlap between fibroadenoma and circumscribed carcinoma which is particularly relevant to younger patients in whom fibroadenoma is more common.

Fine-needle aspiration cytology was the best single investigation in this series, with an indication of malignancy in 93 per cent of patients and a specificity of 100 per cent, the latter being in accordance with our previous reports when adequate smears were obtained[4,5,11].

The cytological sensitivity in this series was higher than previously reported for women of all ages[10], but the difference was not statistically significant. Review of the five cytology reports scored as +1 showed that there was a tendency to reduce the score because of the patients' age: none were particularly well differentiated or poorly cellular which are the reasons for ascribing a +1 score to a positive aspirate. Similarly, review of the four aspirates that were scored 0 reveals two which were consistent with carcinoma on review, reflecting a reluctance to give a positive report. The percentage equivocal was 13 per cent compared with 3·8 per cent for all ages[10]; the difference is statistically significant.

The good fine-needle cytology results may be due to the fact that so few tumours were well differentiated or densely scirrhous. Although there is a wide difference in Bloom's grades ascribed to tumours by different authors, considerable consistency can be achieved both within and between observers[13]. Good consistency of observations (87 per cent) has validated the difference between the two groups of tumours in this study. This finding agrees with Brightmore *et al.*[14] who found an increased proportion of high grade tumours in young women and with Charleston and Feinstein[15] who found evidence for a more rapid growth rate in tumours from premenopausal women.

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CA15-3: its relationship to clinical stage and progression to metastatic disease in breast cancer

There is increasing interest in the potential role of monoclonal antibodies as tumour markers in the early detection of metastatic disease. CA15-3 is a circulating antigen which is relatively specific for breast tissue and defined by two monoclonal antibodies. It is elevated in the serum of patients with breast cancer but its relationship to clinical stage and tumour progression has not been well defined. CA15-3 levels have been measured in a consecutive series of 97 patients with breast cancer at the time of diagnosis and at 3-monthly intervals thereafter. All patients have been evaluated and followed by using routine biochemical and radiological parameters to detect occult metastatic disease. There was no difference between a control group of patients who presented with benign disease ($n=18$: *mean(s.d.) 18·0(5·1) units/ml): and those who presented with stage I disease* ($n=37$: *18·4(5·3) units/ml) or stage II disease* ($n=21$: *18·0(4·0) units/ml). Patients with stage III disease* ($n=23$: *32·0(10·4) units/ml) had significantly elevated levels of CA15-3 compared with those in stage I* ($P<0{\cdot}001$). *All patients with documented metastatic disease at presentation or at follow-up had markedly elevated CA15-3 levels* ($n=10$: *155·8(50·2) units/ml). CA15-3 is a reliable tumour marker in patients with advanced disease.*

Keywords: Breast cancer, CA15-3, tumour markers

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Despite the widely accepted use of tumour markers such as carcinoembryonic antigen as a means of early detection of metastatic disease in colorectal cancer there has to date been no satisfactory tumour marker for breast cancer which is the commonest malignancy in females. Detection of metastatic disease from breast cancer is presently dependent on clinical examination, non-specific biochemical serum analysis and radiographic techniques. Recent advances in the detection of tumour-specific monoclonal antibodies have made available potential markers for metastatic disease. CA15-3 is a circulating antigen expressed by human breast tissue and is defined by two monoclonal antibodies: DF3, which is found on the surface of mammary carcinoma cells, and 115D8 which is found on milk-fat globule membrane[1,2]. It is relatively specific for breast cancer but its precise role has not been firmly established[3]. This study was prospectively undertaken to define the correlation between the level of CA15-3 and clinical stage of disease in order to determine what part this tumour marker has to play in the follow-up of patients with breast cancer.

Patients and methods

Since October 1986 all patients who presented to the breast clinic at University College Hospital, Galway with carcinoma of the breast were entered into the study. Serum levels of CA15-3 were taken from 18 patients who had benign breast disease in order to determine a normal reference value for this laboratory (mean(s.d), 18 0(5·1) units/ml). Measurements were taken using a commercially available radioimmunoassay kit (ELSA CA15-3, International CIS, Saint Quentin, France) employing a solid phase two-site immunoradiometric assay. Briefly, 25 μl of the patients blood is incubated in a test tube containing the antibody 115D8 coated in solid phase for 1 h at 37°C. The tube is washed and the tracer antibody DF3, labelled with radioactive iodine, is then added The tube is again incubated at 37°C for 1 h After washing, the bound radioactivity is measured using a γ counter CA15-3 levels are then measured from a standard curve, coefficients of variation of the assay are ±8 per cent.

Ninety-seven patients with breast cancer were entered in the study: 35 were premenopausal and 62 were perimenopausal or postmenopausal. The average age was 54 years (range 24–89 years)

The patients were staged according to the standard UICC (International Union against Cancer) breast cancer classification. At presentation 37 patients were in stage I, 21 were in stage II, 23 were in stage III and five were in stage IV Eleven patients presented with disease progression having had definitive surgery for breast cancer before the study period: eight of these had local recurrence confined to the chest wall and three had disseminated metastatic disease.

CA15-3 levels were measured at presentation in all patients and again at 1 month postoperatively. Patients were followed up at 3 months postoperatively and subsequently at 3-monthly intervals.

All patients were screened for metastatic disease with chest radiographs, liver function tests and bone scan at first presentation. Whenever there was a clinical suspicion of metastatic disease at follow-up the screening tests were repeated

Levels of CA15-3 in different stages of disease were compared with levels in patients with stage I disease by analysis of variance. Serial CA15-3 levels at follow-up in all groups were compared with preoperative levels. Statistical significance was taken at the $P<0\ 05$ level

Results

There was no difference between the levels of CA15-3 in those with benign lesions of the breast (mean (s.d.), 18.0(5·1) units/ml) and patients with stage I (18·4(5·3) units/ml) or stage II (18·0(4·0) units/ml) cancer or locally recurrent disease (23·0(8 0) units/ml; *Table 1*). Patients with stage III or IV disease had significantly elevated levels of CA15-3 compared with either the control group or those with stage I disease ($P<0{\cdot}001$). Only 4 per cent of patients with stage I or II disease demonstrated levels of CA15-3 greater than 25 units/ml in this study and no patient in these groups had a preoperative level greater than 30 units/ml. Eighty-three per cent of patients with stage III disease had preoperative levels of CA15-3 greater than 25 units/ml.

A comparison between preoperative CA15-3 levels in patients with stage III disease and postoperative levels at 3, 6 and 12 months demonstrated a progressive decrease which was statistically significant (*Figure 1*).

At presentation five patients had stage IV disease and three others presented with metastatic disease having been diagnosed and treated before the study period. Two additional patients have progressed to metastatic bone disease which was confirmed on bone scan in the course of the study. One of these had stage II disease at presentation (CA15-3 level: 17·0 units/ml) and the other was in stage III at presentation (CA15-3 level: 28·5 units/ml). Both patients have demonstrated elevated levels

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Table 1 *Preoperative serum CA15-3 levels in 18 patients with benign breast disease and 97 patient with breast cancer*

Stage of disease	Number of patients	Preoperative serum CA15-3 level (units/ml)
Benign	18	18·0(5·1)
Stage I	37	18·4(5·3)
Stage II	21	18·0(4·0)
Stage III	23	32·0(10·4)
Stage IV	5 (+3)*	155·8(50·2)
Local recurrence	8	23·0+8·0

Values are mean and s.d. * These three patients presented with disease progression to metastases having had definitive surgery for breast cancer before the study period

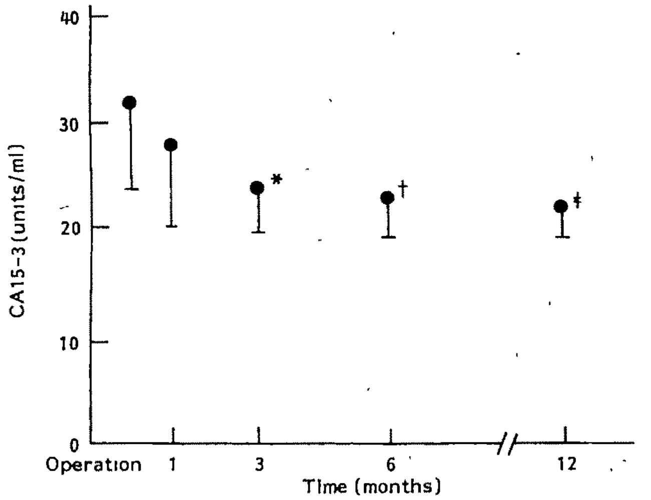

Figure 1 *Serial postoperative serum CA15-3 levels (mean and s.d.) in patients with stage III breast cancer.* *P<0·02, †P<0·003, ‡P<0·001 *(analysis of variance)*

of CA15-3 on follow-up and one had a markedly elevated CA15-3 level (113·5 units/ml) at a time when, although she complained of bone pain, her bone scan was negative. Repeat bone scan 3 months later confirmed the presence of metastases (*Figure 2*). No patient with distant metastases had a level of CA15-3 below 50 units/ml and in over 85 per cent of this group the levels were greater than 150 units/ml.

Discussion

Serum CA15-3 levels have been determined previously in healthy controls[4] and in those with carcinomas of other organs and elevated levels have been shown to be relatively specific for breast cancer. Previous studies have confirmed that the levels of CA15-3 are not affected by the age of the patient[4]. The levels among patients with benign disease and stage I and II disease correlate well with the results from other laboratories[3,4]. Several circulating antigens are elevated in association with breast cancer[5–8], but none of these have gained widespread use. Carcinoembryonic antigen has been shown to correlate with change in breast disease status[9] but it is not specific unless patients have hepatic metastases[10]. It has previously been demonstrated that CA15-3 is significantly more sensitive than carcinoembryonic antigen in the evaluation of patients with both primary and metastatic breast cancer[3].

In this study CA15-3 levels correlated with the stage of disease. CA15-3 was not elevated in benign breast disease or stage I or II disease and is not of any value in the detection of early or occult breast cancer. The progressive reduction in CA15-3 levels postoperatively in stage III disease may reflect the decrease in tumour burden. The fact that the decrease is not significant until 3 months after operation may reflect the long half-life of the antigen, the excretory kinetics of which have not yet been established. Moreover, in patients with metastatic disease all of the levels were markedly elevated while those in patients with locally recurrent disease were not, again suggesting that this marker reflects tumour burden. At follow-up the patients with metastatic disease showed neither a clinical response nor a drop in serial CA15-3 estimations

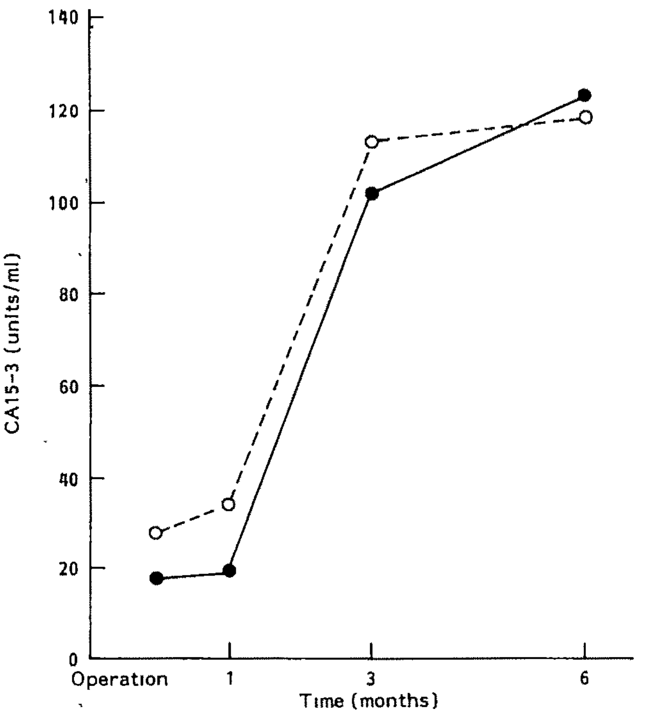

Figure 2 *Serial CA15-3 levels in two patients who developed metastatic disease to bone: +ve, bone scan positive in this patient, −ve, bone scan negative in this patient*

In the future, serial CA15-3 estimations may be used to detect metastatic disease earlier than currently available methods, as occurred in one case in our series. The analysis is simple, more practical and much less expensive than currently available methods.

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Additional value of fine-needle aspiration biopsy in a mammographic screening trial

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The Stockholm breast cancer screening trial used single-view mammography as the sole screening method. A majority (63 per cent) of the mammographic selected cases from the first two screening rounds had uncertain mammograms, coded as 3 on an ordinal scale from 1 to 5, where 1 and 2 are dismissed as normal mammograms and 5 stands for a typical cancer. In this group of uncertain mammograms 30 cases were malignant and 431 were non-malignant. The aim of this study was to examine whether surgical biopsy in this group could be replaced by fine-needle aspiration (FNA) biopsy, combined with the information from the mammogram and clinical examination, and whether this diagnostic strategy could select the malignant cases with a high sensitivity. FNA biopsy selected 25 of the 30 mammary carcinomas as definite malignancy or atypia, with a sensitivity of 83 per cent (95 per cent confidence interval: 69–96 per cent), and combined with the information from the mammogram and clinical examination 29 of the malignancies were selected with a sensitivity of 97 per cent (95 per cent confidence interval: 83–100 per cent). In 398 of 431 non-malignant cases the diagnosis was established with the triple diagnostic approach without needing a surgical biopsy. In a clinical follow-up study, up to 64 months after the first screening round, only one false negative case was found, included in the group of 30 malignancies described above. With this strategy the rate of negative surgical biopsies was reduced by 90 per cent in the group with uncertain mammograms and without considerably impairing the reliability of the results.

Keywords: Breast biopsy, mammography, screening, fine-needle aspiration biopsy

If mammographic screening for early detection of breast cancer is to result in the intended decrease in mortality rates, the quality of the screening mammography and the clinical investigations need to be high, otherwise a large number of unnecessary open surgical biopsies will be performed at great cost and with anxiety among the selected women[1–3]. Quality control is particularly important when nationwide screening projects are planned, based on results from the early randomized trials in the USA, The Netherlands and Sweden[4–13].

In screening programmes there is always a large group of selected women whose mammographic findings are uncertain. There is not enough evidence to justify surgery but the mammogram is not normal. Without unlimited resources, these women either have to be submitted to surgery or classified as normal without surgical biopsy and without a time-consuming clinical follow-up.

The Stockholm screening trial began in 1981 and included 60000 women aged 40–64 years. Single-view mammography was the only screening method used and the selected cases were recalled for complete mammography. The mammograms were classified on an ordinal scale from 1 to 5, where 1 indicates a normal mammogram and 5 a typical cancer. Women with codes 1 and 2 have usually been dismissed as normal, while those with codes 4 and 5 have had a surgical biopsy. In the first and second screening rounds 67 and 56 per cent respectively of the selected cases with a complete mammography were classified as code 3 Together with the women with codes 4 and 5 they were recalled for clinical investigation and fine-needle aspiration biopsy (FNA).

The aim of this study was to evaluate the ability of FNA biopsy to detect the small number of malignant cases in the large group of screening-selected women with small pathological mammographic findings. A secondary aim was to determine whether FNA biopsy together with clinical examination and complementary mammography are reliable enough to assure the selected women that their mammographic finding is non-malignant, without support from a negative surgical biopsy.

Patients and methods

Screening programme

A mammographic screening programme was begun in 1981 in south-east Stockholm The population comprised 60000 women aged 40–64 years, of whom 40000 were offered mammography and 20000 functioned as a control group The project and the first round results have been described in detail[14]. The screening was done with an oblique, single-view mammographic projection according to Lundgren and Jakobsson[15]. Participation rates exceeded 80 per cent in both the first and the second screening, with small differences between age groups. The incidence of recalls for further examinations, with results from the first two screening rounds, are given in *Table 1*.

Patients

This study comprises 727 women, selected from the first two screening rounds in the Stockholm screening project Further investigation led to the diagnosis of 223 cancers and 504 non-malignant cases. Of the 504 non-malignant tumours, 398 were classified with FNA biopsy, clinical palpation and mammography, without needing a diagnostic surgical biopsy. Of the 223 mammary carcinomas, 194 cases (87 per cent) were selected with codes 4 or 5, and 29 cases with code 3 at mammography.

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Table 1 *Course of events in the first and second screening rounds*

	First screening	Second screening
Number of participants in screening	32 555	30 765
Complete mammography	1 655 (5·1)	989 (3·2)
Clinical examination and fine-needle aspiration biopsy	482 (1·5)	246 (0·8)
Surgery	207 (0·6)	122 (0·4)
Histological diagnosis of malignancy	128 (0·4)	95 (0·3)
Histological diagnosis of benign disease	79 (0·2)	27 (0·1)

Figures in parentheses are percentages of participants

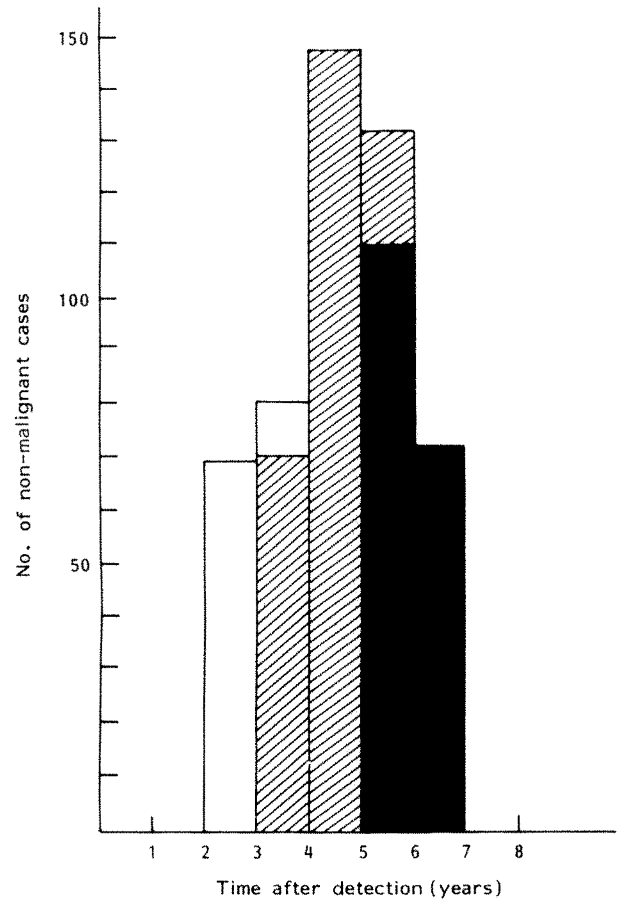

Figure 1 *Clinical follow-up of the non-malignant tumours detected in the first two screening rounds, showing the number of rescreenings after detection:* □, *no rescreening after detection;* ▨, *one rescreening after detection;* ■, *two rescreenings after detection*

Methods

Mammography. A single oblique view by the Lundgren technique was used for screening[15]. If malignancy was suspected the patient was subjected to a conventional three-view mammogram, as stated previously. The complete mammogram was classified, depending on the suspicion of malignancy, from 1 to 5 where 1 and 2 represent a benign lesion, 3 represents a middle group, 4 represents a high suspicion of malignant lesion, and 5 represents a typical cancer.

Triple diagnostic procedure. All selected cases from the screening programme were remitted preoperatively for triple diagnostic procedure, including clinical investigation, FNA biopsy and complementary X-ray, in order to classify the tumour as malignant or non-malignant.

Tumour sampling. FNA biopsy was performed for the cytological diagnosis[16]. A stereotaxic device was used if the tumour was not palpable[17,18]. If the aspirated material was not conclusive, the tumour was excised under general anaesthesia after preoperative localization, carried out in collaboration with the responsible radiologist and guided by the mammogram. The position of the lesion was indicated on the breast with waterproof ink, in accordance with its position on the craniocaudal and lateromedial projections on the mammogram. The surgical specimen was radiographed peroperatively to ensure that the mammographically suspected lesion had been removed[19,20]. The tumour was indicated with a needle to guide the pathologist[19,20]. In some cases, if the aspirated material from the FNA biopsy was not conclusive, and the suspicion of malignancy in the screening-detected lesion was very low, the patient was followed clinically with a new mammogram and sometimes with a new FNA biopsy without a diagnostic surgical biopsy. If the diagnosis of carcinoma was established cytologically, the operation was performed without further diagnostic procedures.

False negative cases. All cases classifed as non-malignant tumour after the triple diagnostic procedure were followed up in the regional cancer registry of Stockholm county; the mean follow-up time was 64 months (median 63 months) after the first screening round and 37 months (median 38 months) after the second round (*Figure 1*). Almost all breast cancers in the Stockholm area are reported to the regional cancer registry.

Results

In the first two screening rounds 728 women (482 in the first round, 246 in the second) were selected and recalled for triple diagnostic procedure (*Table 1*). One case in the first screening round refused further investigations.

The group of mammographically highly suspected lesions (codes 4 and 5) totalled 266 cases: in 194 of these the tumour was malignant and in 72 it was non-malignant. The figures for the first and second screening rounds are given in *Figure 2*. In 79 per cent (141 of 178) of the malignant lesions a preoperative

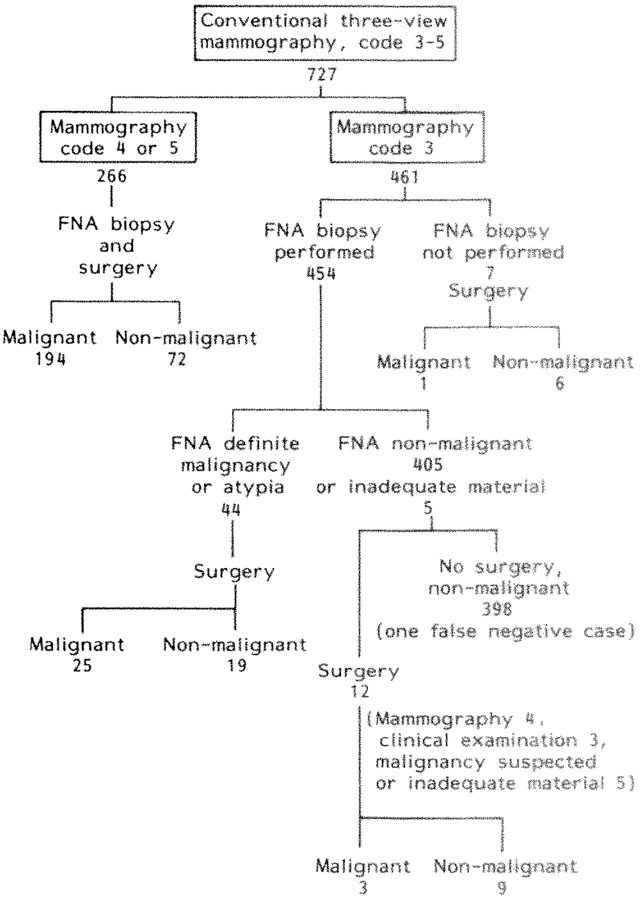

Figure 2 *Comparative flow scheme of the diagnostic procedure in the first and second screening round, in relation to mammography code. FNA, fine-needle aspiration*

FNA biopsy classified the cytology as cancer or suspected cancer. In 16 cases of malignancy the diagnosis was established with surgical biopsy without a preoperative FNA biopsy. Surgery was performed in all but seven of the cases with mammography codes 4 and 5.

The group of mammographically less suspicious lesions (code 3) totalled 461 cases from the first two screening rounds. In 30 cases the tumour was malignant and in 431 it was non-malignant (*Figure 2*). During a clinical follow-up one of the non-malignant cases turned out to be a mammary carcinoma, described below (*Figure 3*). FNA biopsy selected 25 of the malignant lesions, with a sensitivity of 83 per cent (95 per cent confidence interval: 69–96 per cent). In three cases FNA biopsy was negative, and in the fourth case FNA biopsy was not performed. The malignant diagnosis in these four cases was established with a diagnostic biopsy, as the mammogram indicated a suspected malignant lesion. With the triple diagnostic approach, 29 of the malignancies were selected with a sensitivity of 97 per cent (95 per cent confidence interval: 83–100 per cent). In 398 cases the non-malignant diagnosis was established with FNA biopsy together with clinical investigations and complementary mammography, without a diagnostic surgical biopsy. In a clinical follow-up study with mean follow-up times of 64 and 37 months after the first and second screening rounds respectively, one genuine false negative case was found. The women have passed none, one or two further screening rounds after the detection of the non-malignant lesion (*Figure 1*). The false negative case turned out to be a non-invasive intraductal cancer, at the following screening mammography 24 months later (*Figure 3*).

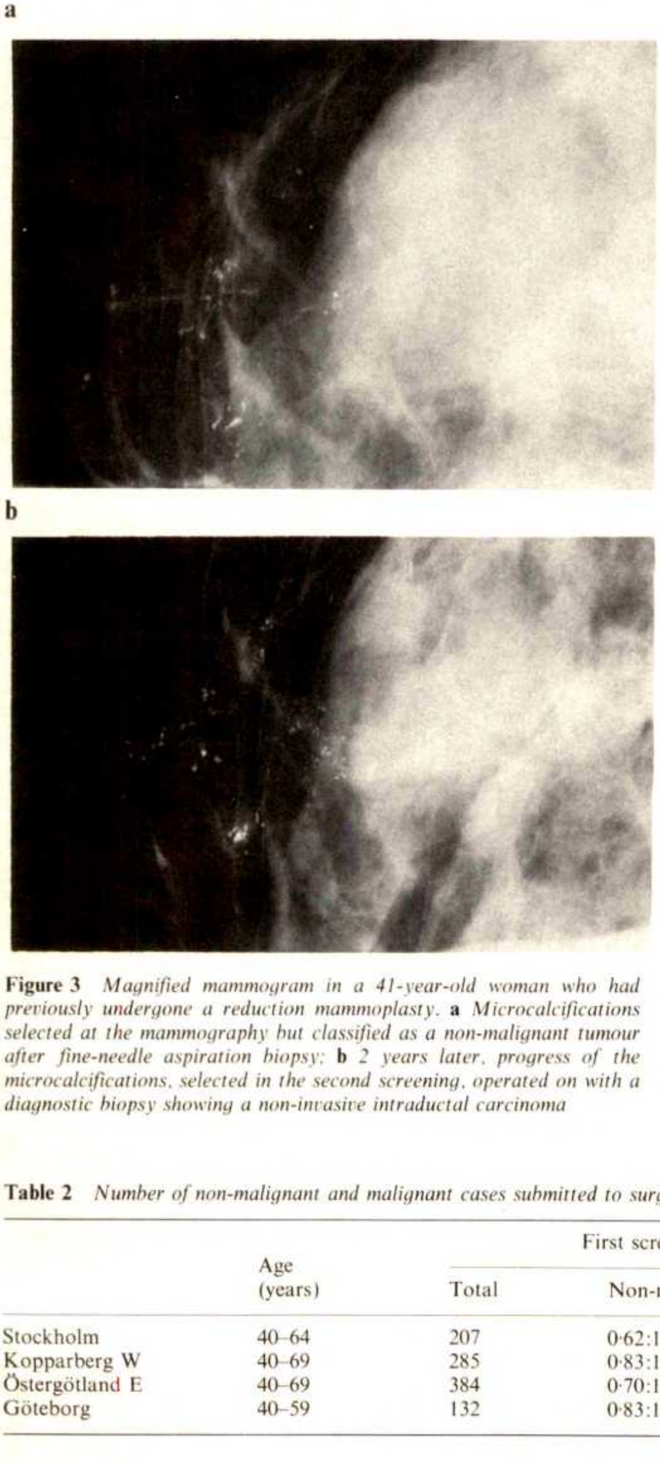

Figure 3 *Magnified mammogram in a 41-year-old woman who had previously undergone a reduction mammoplasty.* **a** *Microcalcifications selected at the mammography but classified as a non-malignant tumour after fine-needle aspiration biopsy;* **b** *2 years later, progress of the microcalcifications, selected in the second screening, operated on with a diagnostic biopsy showing a non-invasive intraductal carcinoma*

The cancer risk in this group of screening-selected women with a classified non-malignant tumour after the triple diagnostic procedure is calculated to be 1·08 (128/32 555 × 274) in the first screening round and 0·40 (95/30 765 × 129) in the second round. The calculated breast cancer risk in this group is 1·5 cancers per woman or 0·75 of a cancer per breast (not significantly different). Two more cancer cases were found in this group but these new cancers emanated from another part of the breast, clearly distinguished from the earlier detected non-malignant lesion.

Table 2 gives the ratio of non-malignant:malignant cases submitted to surgery in four Swedish trials. The rate of non-malignant lesions is falling in the screening rounds that follow the prevalence screening. One reason for this is that many of the benign lesions are selected in the first round. Another is that the radiologist has an earlier mammogram for comparison in subsequent screening rounds.

Discussion

A high proportion of women, 73 per cent and 61 per cent of those selected in the first and second screening rounds respectively, and submitted to the triple diagnostic procedure after complete mammography, had a non-malignant disease. This is in good agreement with the results from the Swedish two-county Study (WE-trial)[21,22].

A high rate of negative biopsies has been reported from North America, with a non-malignant:malignant ratio of 6:1 at biopsy in the Breast Cancer Detection Demonstration Project (BCDDP)[1].

It is desirable that the majority of the non-malignant lesions can be classified as normal not only without diagnostic surgery, but also without an increased number of cases that turn out to be false negative.

In all Swedish screening trials FNA biopsy is frequently used in the triple diagnostic procedure for all selected cases. FNA biopsy was performed in all but a few cases in the Stockholm trial.

Of the screening-selected cases with highly suspicious mammograms (codes 4 or 5), almost all were submitted to surgery, even if the cytology was negative. In this group a preoperative FNA biopsy selected 79 per cent of the malignant tumours in the first two screening rounds as definite or highly suspected cancers. The advantage of a definitive preoperative cancer cytology result in this group is that cancer surgery can be performed from the beginning of the operation, without requiring diagnostic procedures such as frozen section analysis or a two-stage operation.

In the other group of selected mammograms (code 3) there

Table 2 *Number of non-malignant and malignant cases submitted to surgery in the first two screening rounds in four Swedish trials*

	Age (years)	First screening		Second screening	
		Total	Non-malignant:malignant	Total	Non-malignant:malignant
Stockholm	40–64	207	0·62:1	122	0·28:1
Kopparberg W	40–69	285	0·83:1	151	0·50:1
Östergötland E	40–69	384	0·70:1	141	0·33:1
Göteborg	40–59	132	0·83:1	49	0·48:1

were 461 cases; FNA biopsy, together with the information from mammography and clinical examination could be most valuable. With use of the triple diagnostic procedure 29 of 30 mammary carcinomas were diagnosed and FNA biopsy alone selected 25 tumours with definite or suspected malignancy with a sensitivity of 83 per cent

In nearly half (46 per cent) of the 30 mammary carcinomas, the mammographic findings consisted in cases of microcalcifications, most of which were non-palpable. This mammographic feature is commonly associated with malignancy[23]. A liberal attitude towards surgical biopsies in cases of selected microcalcifications on the mammogram, despite a negative cytology result, is recommended.

At the clinical follow-up only one false negative case could be detected (*Figure 3*) This case, with microcalcification on the mammogram, was classified as a non-malignant tumour at the first screening, but was diagnosed as a non-invasive mammary carcinoma 2 years later in the following screening round. Follow-up of the non-malignant cases diagnosed with triple diagnostic procedure, without surgical intervention, could be an important feedback on the effectiveness of the diagnostic methods used in a screening programme.

Full evaluation of a breast cancer screening programme should take into account the undue anxiety generated in the selected women with non-malignant lesions and the psychological harm of having to undergo negative surgical biopsies[1–3].

Table 2 gives the ratio of non-malignant:malignant cases submitted to surgery in four Swedish trials. In all trials in Sweden, the two trials in The Netherlands and the Guildford (UK) trial, the rate of 'unnecessary' surgical biopsies is reported to be low[21,22,24,25], in contrast to the figures from North America and a few additional centres in the UK[1,26,27].

In the Stockholm trial the rate of unnecessary surgical biopsies among selected cases with code 3 mammograms was reduced by 90 per cent using only FNA biopsy, clinical examination and information from the mammogram and without impairing considerably the reliability of the results.

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Review

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Postoperative gastric ischaemia

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This review discusses postoperative gastric ischaemia after detailed consideration of the gastric blood supply and the effects of devascularization. Special consideration is given to gastric remnant necrosis, lesser curve ischaemia after highly selective vagotomy, and gastric ischaemia after other operations.

Keywords: Stomach, blood supply, postoperative ischaemia

Because of its abundant blood supply, the stomach has traditionally been held to be resistant to postoperative ischaemia. However, with the development of a large variety of operations which interfere drastically with the gastric blood supply, postoperative gastric ischaemia has been increasingly recognized. In this review, an outline of the gastric blood supply is given, the experimental basis for the occurrence of ischaemia is adduced, and the clinical syndromes of postoperative gastric ischaemia are examined.

Gastric blood supply

The arterial blood supply to the stomach, as outlined in the standard surgical texts, seems quite simple There are five sources of arterial supply which are held to be fairly constant. The coeliac trunk is the main contributor and gives rise to the following vessels: the left gastric artery, which is a direct branch of the coeliac trunk, the right gastric artery, which is usually a branch of the hepatic artery; the right and left gastroepiploic arteries, which originate from the gastroduodenal and splenic arteries respectively; and the short gastric arteries, which arise from the splenic artery.

In a study of 200 human cadavers, Michels[1] pointed out the limitations of the classical model by demonstrating the part played by at least six additional arteries. the superior pancreaticoduodenal, the superior duodenal artery of Wilkie, the retroduodenal, the transverse pancreatic, the dorsal pancreatic and the left inferior phrenic. Suzuki *et al.*[2] drew attention to the posterior gastric artery, described under various appellations by different authors. It was found arising from the superior aspect of the mid-third of the splenic artery in 62 per cent of cadavers. Its nutritional supply to the superior portion of the body and the fundus may be crucial to the viability of the stump after high gastrectomy and of the fundus after splenectomy. The contribution of the oesophageal arteries to the supply of the stomach is well documented in large anatomical studies[3,4] The extreme variability of the arterial supply to the stomach has been studied and an attempt has been made at codifying it in several types[5].

A better understanding of the intrinsic circulation may help to clarify the issue of gastric ischaemia. Two notable features are the absence of gastric end-arteries and the freely anastomotic nature of the intramural vessels[6] Complete filling of all the intramural vessels has been obtained in the cadaver by injection of any major artery after ligation of all the other extramural vessels; even the injection of a single short gastric artery seems to suffice. Such studies have supported the conclusion that 'The margin of safety in gastric operations involving mobilization of the stomach with ligation of major extramural vessels is probably as great or even greater than has been believed, and this fact should lend security in those instances in which such procedures are necessary '[7]. The clinical rarity of spontaneous gastric infarction is therefore not surprising. Cohen reported three cases of total gastric infarction but could not find any similar reports in the literature[8] However, thrombosis of the portal system or the coronary vein[9] are well documented causes of partial infarction of the stomach.

In the anterior and posterior walls of the body of the stomach, the rich mucosal plexus arises from a plexus of large submucosal vessels which in turn is supplied by branches from the extragastric arterial arcades. The lesser curvature is peculiar in this respect as its mucosal plexus is supplied directly from the extragastric arcades[6] As early as 1920, Reeves[10] emphasized the finer calibre and the smaller number of the anastomoses between adjacent branches in the lesser curvature region, resulting in their greater resistance to flow and predisposition to thrombosis. Piasecki[11] studied the vascular supply of normal stomachs and showed that some persons had patches of mucosa supplied by end-arteries. Because these patches occurred on the usual ulcer-bearing areas, he suggested that ischaemia plays a role in the initiation of peptic ulceration. Two studies provide extensive bibliographies on this theory[12,13].

Effects of experimental and surgical devascularization

The bulk of the experimental work on gastric devascularization was performed to assess its effects on gastric secretion, but the consequences of such procedures on gastric viability were also noted. In dogs, the effects of ligation of some or all of the vessels on the lesser curvature, greater curvature, or both curvatures were studied[14]: only complete devascularization of both curvatures resulted in gangrene of the stomach, and it was noted that the ischaemic injury affected only the greater curvature. This tolerance to partial gastric devascularization in the dog was confirmed but the ligation of all four major arteries was lethal[15]. Further work demonstrated that the preservation of the oesophageal arteries and a minor branch of the left gastric was sufficient to guarantee gastric viability, provided venous flow was not impeded[16]. A recent experimental study[17] demonstrated the resilience of the stomach to extensive devascularization by establishing a return to normal of the mucosal blood flow within a week.

In man, extensive surgical devascularization has been advocated from time to time. Somervell[18] performed 5000 'physiological gastrectomies' this operation involved the ligation of a large proportion of the gastric arteries on the assumption that hyperacidity would be relieved and recurrent ulceration prevented after gastroenterostomy; the problem of ischaemia is not even raised in his report. Ligation of the hepatic, splenic and left gastric arteries was also performed in a series of patients in an attempt to alleviate advanced portal cirrhosis[19], without resulting in ischaemia. An even more thorough devascularization, which left the stomach literally 'hanging on the right gastroepiploic artery' (and included a splenectomy), has also been recommended in portal hypertension[20]. Massive haemorrhagic gastritis was considered to be another indication for four-vessel ligation[21,22] and, even in instances where the spleen had already been removed, ischaemia did not complicate the procedure[23].

Postoperatic gastric ischaemia

Gastric remnant necrosis

In 1953, Rutter[24] was the first to report a case of ischaemic

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necrosis of the gastric remnant following subtotal gastrectomy. The possibility of such a complication had been previously discounted: the surgeon was advised to divide the vessels 'until he deems a sufficient length has been denuded'[25] and it was suggested that 'the line of section is made so as to leave a small devascularized remnant'[26].

The precise incidence of postgastrectomy necrosis is difficult to determine. Only 20 cases could be traced in a review[27] in 1966. Gastric remnant necrosis occurred twice in one series of 604 cases of gastric operations[28] and four times in a personal series of 2000 gastrectomies[29]. Nevertheless, it is to be suspected that leakage at the gastroenteric anastomosis, a more common complication, may be due to relative ischaemia of the gastric remnant sufficient to impair healing but insufficient to produce overt gangrene. Such a hypothesis was put forward by several authors[27,28,30]; viewed from this perspective, the incidence of clinically significant gastric stump ischaemia would become more impressive.

Two experimental studies address the issue of the viability of the gastric stump after partial gastrectomy. Cate and Dawson[31] subjected dogs to a Billroth I gastrectomy of variable extent after ligation of all the major arteries to the stomach at their origin and splenectomy. The larger the remnant, the greater was the risk of necrosis: 20 per cent gastric remnants were associated with a 20 per cent incidence of necrosis, which increased to 80 per cent with 60 per cent residual gastric pouches. The ischaemic necrosis occurred uniformly on the greater curvature. Additional dissection around the oesophageal hiatus (and inevitable division of collaterals originating from the left inferior phrenic artery) increased the incidence of necrosis. Kilgore *et al.*[28] performed a 70 per cent gastrectomy and Billroth II anastomosis in dogs, with ligation of various combinations of arterial sources. Their study indicated that the risk of gastric remnant necrosis is high unless either or both the vasa brevia and the trunk of the left gastric artery are preserved

The clinical features of this complication and the means to prevent it are outlined in several reports[27–29,32–37] and in some textbooks[38,39]. It usually occurs between the 2nd and the 10th day. Its clinical presentation is that of general toxicity or septic shock in conjunction with peritonitis or a gastrocutaneous fistula. The latter, in isolation, represents a less severe degree of ischaemia. It is often difficult to foresee the occurrence of this complication. At operation, a pale or mottled appearance of the gastric remnant may well be a harbinger of ischaemic necrosis. However, it has been pointed out that the intraoperative recognition of the 'blue stomach syndrome' is not always followed by anastomotic leak or remnant ischaemia[40] and, on the other hand, a viable appearance is no guarantee against subsequent necrosis.

It is important for the surgeon to remember that the blood supply to the gastric remnant comes from three sources: the left gastric artery and its oesophageal branches, the splenic artery and its vasa brevia, and the left inferior phrenic artery. It seems essential to preserve one of these sources at the very least. For example, in a high gastrectomy with splenectomy for carcinoma, the left gastric is ligated at its origin together with the splenic artery: the frail phrenic branches constitute the only blood supply to the stump This situation is particularly precarious because in 2·6 per cent of patients, the left phrenic artery is a branch of the left gastric[41]: evidently, ligation of the latter at its origin may prove catastrophic Dissection at the gastro-oesophageal junction (in the performance of a truncal vagotomy, for example) may cause damage to the left inferior phrenic artery. Elderly and atherosclerotic patients may be particularly prone to ischaemic necrosis. Some authors have categorically stated that 'if the left gastric artery has been ligated proximal to its bifurcation and the spleen has been removed, the blood supply to the stomach has been so compromised that the surgeon is committed to total gastrectomy'[42].

The treatment of remnant necrosis calls for prompt reoperation and total gastrectomy. Although conservative treatment has occasionally proved successful, it is generally felt that a gastrocutaneous fistula caused by a significant area of necrosis is unlikely to respond to such a treatment[39]. In a collected series[37], the mortality rate of remnant necrosis was 70 per cent.

Lesser curvature ischaemia following highly selective vagotomy

Ischaemia of the lesser gastric curvature is a rare complication of highly selective vagotomy and most of the publications deal with isolated cases. In 1975, Johnston[43] reported only ten cases in a collected series of 5539 patients having highly selective vagotomy, an incidence of 0·2 per cent In 1983, Couinaud[44] studied this complication extensively in 45 patients, including two personal cases.

The pathogenesis of lesser curve ischaemia is probably multifactorial. The relative deficiency in the blood supply to this area of the stomach has already been mentioned. Multiple experimental studies[45–50] have demonstrated a reduction in the gastric mucosal blood flow after truncal or selective vagotomy, arguably caused by the opening of intramural arteriovenous communications. Several factors may contribute to the occurrence of this complication; they can be divided into three groups which relate to the patient's medical background, the type of operation performed (especially when other procedures are added to the vagotomy), and the technique of the highly selective vagotomy.

Old age has been incriminated as a risk factor[51] but, in Couinaud's review, 23 of the 29 patients whose age was known were under 60 years old[44]. Chronic conditions such as renal failure, hypertension, arteriosclerosis and diabetes mellitus have also been listed as risk factors and, for some[51], they constitute contraindications to the performance of highly selective vagotomy. This view is not shared unanimously Ischaemia has occurred in a few cases after highly selective vagotomy performed for a bleeding ulcer[44,52,53]; whether this constitutes an increased risk is not certain.

The incidence of this complication may well be increased when other procedures are added to the vagotomy. Because duodenal ulcer and gastro-oesophageal reflux often coexist, the combination of highly selective vagotomy and Nissen fundoplication has been advocated[54,55]. Furthermore, it has been claimed that the necessary sacrifice of some of the vasa brevia could be performed with impunity[55]. In a series of 33 such combined operations, three cases of lesser curve necrosis occurred, while there was only one such case in over 400 highly selective vagotomies performed by the same authors[56]. A similar observation was made by Kalsbeek who added a fundoplication to treat an accidental distal oesophageal tear[57]. The pathogenesis of this complication after the addition of fundoplication is unclear. Division of short gastric vessels was not performed in some of the cases[56]. A possible explanation may be massive gastric distention[56]; this is more likely to occur after fundoplication, a procedure well known to interfere with vomiting and belching. There is, in fact, some evidence that gastric distention decreases the arterial flow to the stomach[58,59], particularly in the lesser curve following highly selective vagotomy[60]. Indeed, the entity of spontaneous rupture–necrosis of the excessively distended stomach is well described[61–65] In the light of this hypothesis, it has been considered important to decompress the stomach routinely by means of a nasogastric tube or gastrostomy after combined highly selective vagotomy and fundoplication[56] The addition of splenectomy has also been incriminated in the occurrence of lesser curve necrosis[44,56]. The importance of splenic preservation in case of minor splenic injury during highly selective vagotomy has been stressed; the recommendation has also been made that the splenic vessels should be divided at the hilum, with preservation of the left gastroepiploic artery and some of the vasa brevia[44].

The operative performance of highly selective vagotomy has been scrutinized in search of an explanation for the occurrence of ischaemia. Caution has been expressed regarding the use of diathermy on the gastric wall[44]. Small bites of tissue must be taken when ligating the nerve fibres to the lesser curve, and 'digging into the muscle' of the lesser curve must be avoided[66]. The routine division of the right gastroepiploic vessels at the proximal border of the antrum is being practised by some authors[67–69] in an attempt to disrupt innervation via the terminal branch of the nerve of Latarjet. This manoeuvre may further impair the arterial supply to the lesser curve and may be inadvisable, especially if a Nissen fundoplication is planned or if splenectomy cannot be avoided[68,69].

Lesser curve ischaemia may manifest itself in one of three ways, depending largely on its degree and extent[44,52,70–80]: gastric perforation, gastrocutaneous fistula or gastric ulceration. Gastric perforation due to transmural necrosis may lead to a generalized peritonitis, usually relatively easy to recognize, or to a left-sided localized abscess which may be mistaken for a pleural or pulmonary complication[44]. It has been suggested that reperitonealization and invagination of the lesser curve may prevent free perforation, should transmural necrosis occur[75,79]. Others fear that this manoeuvre could further impair the precarious blood supply of the lesser curve[44].

The postoperative recovery after highly selective vagotomy is usually rapid: the diagnosis of perforation must be entertained in the face of any delay in the patient's postoperative progress. The diagnosis may be readily established by means of a Gastrografin® (Schering Health Care Ltd , Burgess Hill, UK) meal. Only prompt reoperation can decrease the otherwise high mortality rate. The choice of the correct surgical option depends on the size of the perforation and the condition of the peritoneal cavity. In favourable cases, excision and suture of the defect may suffice[73]. If a large area of lesser curve is involved, partial gastrectomy with excision of the ischaemic gastric tissue in its entirety is preferable[74]. In less serious cases of ischaemia, a gastrocutaneous fistula may develop[72]. In the absence of signs of intraperitoneal soiling, a trial of conservative treatment may prove successful but surgery is indicated if this fails.

Gastric ulceration developing after highly selective vagotomy probably represents the least severe form of ischaemia. These ulcers may be large and symptomatic, sometimes causing upper gastrointestinal haemorrhage, days[80], weeks[56], or even months[56,57] after the vagotomy On the other hand, gastric ulcers may be asymptomatic. they usually appear as small, shallow erosions at routine endoscopy[68,69,77]. The large, symptomatic ulcers respond poorly to medical treatment and the majority of them require gastrectomy[44]. Asymptomatic, superficial erosions can be managed conservatively with endoscopic surveillance until healing[68,69,77]. Routine endoscopy after highly selective vagotomy is practised by some authors[44,76] but its place remains uncertain

Gastric ischaemia following other operations

Gastric ischaemia is an infrequent complication of various upper abdominal procedures. In the literature, it is not emphasized to any great extent after operations such as the devascularization procedures used in portal hypertension. It is only sporadically reported after reoperations on the stomach for persistent or recurrent disease: for example, fundoplication may be hazardous even when undertaken years after a selective vagotomy and antrectomy[81] It is possible that its incidence has been somewhat underestimated because anastomotic leaks have not been explicitly acknowledged as a manifestation of ischaemia[39] There are, however, a number of operations where ischaemia is a more frequent cause of postoperative complications. These are discussed briefly.

Splenectomy. Harrison *et al.*[82] reported four personal cases of gastric fistula following splenectomy and collected 14 others from the literature. Ligation of the vasa brevia results in a significant decrease in blood supply to the apical segment of the greater curvature. Operative trauma and ischaemia, often in combination, were found to be the most important factors in the occurrence of this complication. If there is any anxiety about blood supply after splenectomy, the area of the greater curve most susceptible to ischaemia should be plicated with broad seromuscular sutures.

Gastric operations for morbid obesity. Gastric restrictive procedures using staplers have become the preferred operative treatment of morbid obesity Anastomotic leaks and gastric perforation are rare, but dreaded, complications[83]. Ischaemia may be an aetiological factor[84]. Cogbill and Moore reported two cases of perforation of the greater curvature of the proximal gastric pouch following a transverse gastroplasty[85]. Ischaemia was incriminated because the site of perforation was devascularized by division of the uppermost vasa brevia. The intraoperative use of intravenous fluorescein to detect ischaemic areas has been advocated. Vertical banded gastroplasty appears to be the safest gastric partitioning procedure, perhaps because it does not interfere with gastric blood supply[84]. A lethal case of perforation after a gastric banding procedure complicated by a splenectomy has been reported[86] and prompted an experimental study in cats, adding further evidence to support the ischaemic aetiology of this complication. If splenectomy becomes inevitable during the performance of a gastric partitioning operation, the procedure is best aborted[86].

Oesophageal surgery. The stomach is frequently used for oesophageal replacement or bypass in benign or malignant diseases. The mobilization of the stomach and its translocation into the thorax or the neck always necessitates the sacrifice of major arterial trunks. In most instances, blood supply is based on the right gastric and right gastroepiploic arteries with an intact intervening arcade. A different blood supply is sometimes preserved in less frequently used procedures. For example, the right gastroepiploic artery alone is preserved in the isoperistaltic gastric tube[87], the left gastric and left gastroepiploic arteries are preserved in the reversed oesophagoplasty[88], and the left gastroepiploic artery alone is preserved in the reversed gastric tube[89]. It is not surprising that ischaemic complications sometimes occur. Frank gastric necrosis has been reported[88] and perhaps it would have been recognized more frequently had all fatal cases come to post-mortem examination. Segmental gastric ischaemia has also been reported as a direct consequence of the use of stapling devices[90].

Conclusions

Despite a rich blood supply to the stomach, postoperative gastric ischaemia does sometimes occur. It is usually due to a combination of unfavourable anatomical circumstances as well as surgical factors. Ischaemia is produced when the capacity of the abundant gastric network of collaterals is exceeded. Frank gastric necrosis is a rare complication. Healing failure of a suture line may be more frequent and some cases may well be caused by unrecognized relative ischaemia. It behoves the surgeon to remember the normal gastric blood supply and its variations. He must also understand the patterns of restricted vascularization inherent to some operations or their combination Reoperation on the stomach by a different surgeon may be particularly hazardous. The high mortality rate associated with this rare but often lethal complication may be decreased by intraoperative attention to the adequacy of the gastric blood supply and appropriate management of doubtfully viable tissue. A high index of suspicion must be maintained postoperatively and should be followed, when indicated, by prompt reoperation.

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Benign non-traumatic inflammatory strictures of the extrahepatic biliary system

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Obstructive jaundice was the presenting feature in 12 patients with benign, non-traumatic strictures of the extrahepatic bile ducts. Ages at presentation ranged from 1·5 to 60 years and 11 were initially referred with diagnoses of malignant strictures. Histological examination, however, showed benign changes of chronic inflammation, with ulceration in seven, which were distinct from those of primary sclerosing cholangitis. All of the patients remain well from 3 to 14 years after surgery. The aetiology of the strictures is not known.

Keywords: Extrahepatic bile ducts, strictures, benign, non-traumatic

Benign, single, non-traumatic inflammatory strictures of the extrahepatic biliary system are very rare and have generally been considered to be a variant of extrahepatic primary sclerosing cholangitis. Primary sclerosing cholangitis is characterized by a chronic inflammatory fibrosis of the biliary tree, which usually affects both the intrahepatic and extrahepatic bile ducts[1]. Diffuse involvement of the extrahepatic ducts alone occurs in 20 per cent of patients[2,3] and rarely the disease has been described as localized to one segment[4–7].

Twelve cases of benign, non-traumatic inflammatory strictures of the extrahepatic biliary system treated between 1975 and 1986 are presented. The pathological and clinical features suggest that they should be regarded as a separate entity and not a variant of sclerosing cholangitis.

Patients and methods

Twelve patients who underwent resection of isolated strictures of the extrahepatic duct have been studied. Clinical and biochemical examination revealed obstructive jaundice in all 12. The age range was 1·5–60 years, and the female:male ratio was 7:5 (see *Table 1*). Investigations included ultrasonography and percutaneous transhepatic cholangiography; endoscopic retrograde cholangiography was also available in three patients. Radiology demonstrated a localized obstructing stricture in the extrahepatic biliary system with dilatation of the intrahepatic bile ducts in 11 of the 12 patients (*Figure 1*). A preliminary radiological diagnosis of malignancy was made in ten of the 12 patients.

None of the 12 patients had evidence of ulcerative colitis, mediastinal or retroperitoneal fibrosis, pancreatitis, orbital fibrosis, immunodeficiency syndromes or Peyronie's disease, all of which are associated with sclerosing cholangitis[4]. The strictures were not associated with gallstones and there was no history of previous surgery, except for one exploratory laparotomy.

All 12 patients underwent laparotomy; in 11, the macroscopic appearances of the extrahepatic biliary system suggested tumour, but in the other (case 9) no macroscopic abnormality was apparent. Seven lesions were excised before hepaticojejunostomy with a Roux-en-Y loop of jejunum. In one, a bypass hepaticojejunostomy was performed primarily. In case 9, with no external macroscopic abnormality, the common bile duct was opened and explored with the choledochoscope. A proliferative lesion was identified at the junction of the right and left hepatic ducts and this was excised with the biopsy forceps. A T tube was left in the common bile duct. In case 12, a small 'tumour' was palpable and was excised by choledochotomy and choledochoscopy.

Two cases were of particular interest and serve to illustrate the 'benign' nature of the clinical course of these lesions. A 15-year-old female patient (case 4) presented initially with painless obstructive jaundice. Percutaneous cholangiography demonstrated an obstructing lesion in the common hepatic duct, at the junction of the right and left hepatic ducts. Laparotomy was performed and an unresectable 'tumour' mass noted. No extrahepatic ducts were available for direct surgery and a biopsy only was performed. This was reported as embryonal rhabdomyosarcoma. She was transferred for further treatment. At repeat laparotomy T tube intubation was performed through the right hepatic duct with relief of the jaundice (*Figure 2*). Further biopsy showed hyperplastic biliary epithelium with underlying cellular granulation tissue including plasma cells and eosinophils. In places prominent spindle cells with eosinophilic cytoplasm were present; the cells were interpreted as myofibroblasts. She subsequently remained well and 2 years later was re-explored. Partial resolution of the mass had occurred and hepaticojejunostomy with a Roux-en-Y loop of jejunum was now possible. She remains well with normal liver function tests and radionuclide excretion scans 5 years after surgery.

A 25-year-old woman (case 6) presented with painless obstructive jaundice in 1975. Percutaneous transhepatic cholangiography demonstrated an obstructing lesion in the common hepatic duct, radiologically indistinguishable from a cholangiocarcinoma. At laparotomy, the mass was unresectable and tube intubation was performed (*Figure 3*). She subsequently remained well and had numerous tube changes. In 1986, tube change under radiological control was technically impossible and a second laparotomy was performed. This demonstrated that the mass had resolved and hepaticojejunostomy was performed with a Roux-en-Y loop of jejunum.

Table 1 *Summary of cases of benign, non-traumatic inflammatory strictures of the extrahepatic biliary system*

Case no.	Sex	Age at presentation (years)	Operation	Follow-up (years)
1	M	1·5	Excision, Roux-en-Y reconstruction	5
2	F	6	Excision, Roux-en-Y reconstruction	10
3	F	13	Excision, Roux-en-Y reconstruction	12
4	F	15	Intubation, subsequent hepaticojejunostomy	7
5	M	24	Hepaticojejunostomy	8
6	F	25	Intubation, subsequent hepaticojejunostomy	14
7	F	34	Excision, Roux-en-Y reconstruction	3
8	M	39	Excision, Roux-en-Y reconstruction	5
9	F	44	Intubation, choledochoscopic biopsy excision	3
10	M	51	Excision, Roux-en-Y reconstruction	12
11	F	55	Excision, Roux-en-Y reconstruction	12
12	M	60	Intubation, choledochoscopic biopsy excision	12

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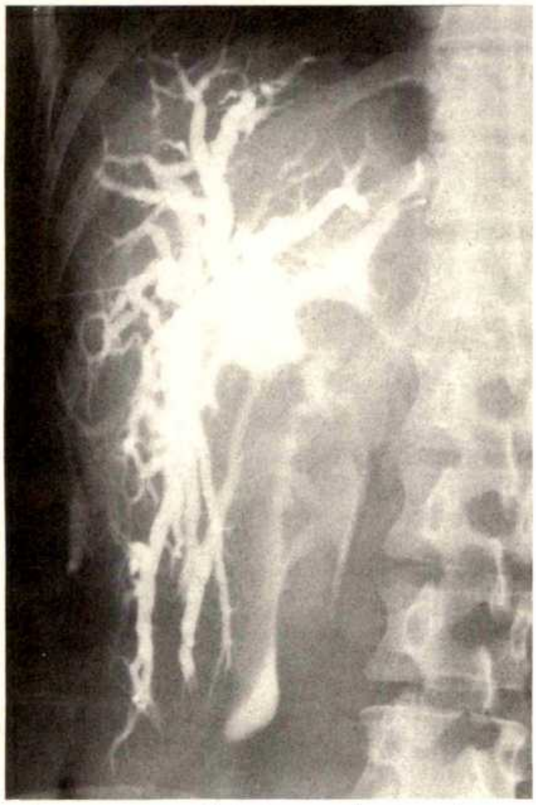

Figure 1 *Percutaneous cholangiogram showing almost complete occlusion of the common hepatic duct in a 55-year-old woman with obstructive jaundice treated with hepaticojejunostomy (case 11)*

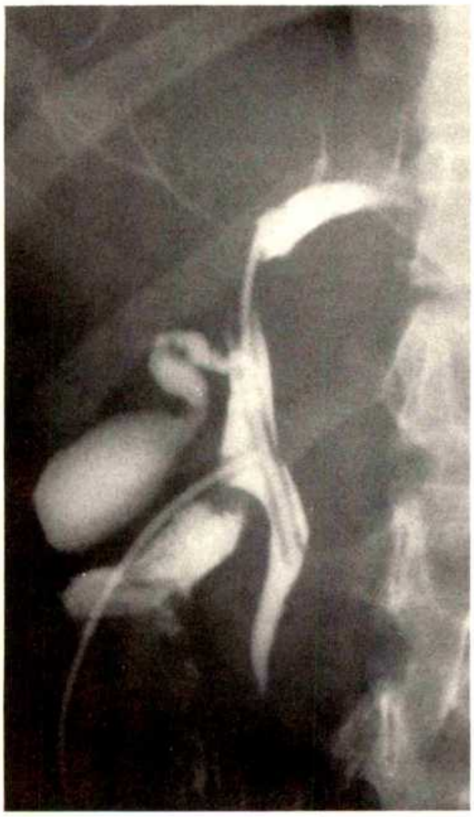

Figure 2 *Stricture of the common hepatic duct in a 15-year-old female patient treated initially with a* T *tube, and later with hepaticojejunostomy (case 4)*

Results

A total of 16 extrahepatic bile duct biopsies were reviewed from the 12 patients (ten common bile duct, five common hepatic duct, one cystic duct).

Four main histological features were seen in the biopsies (*Figures 4* and *5*).

1. *Chronic inflammation*: evidence of chronic inflammation was present in all biopsies but varied from a mild, patchy, predominantly perivascular infiltrate of lymphocytes and plasma cells in some cases to solid sheets of lymphoid cells in others. A few biopsies contained eosinophils and/or histiocytes but these were always a minor component compared with the lymphocytes and plasma cells. Very few biopsies contained polymorphs.
2. *Ulceration*: seven of the biopsies showed extensive ulceration of the surface epithelium while a further six showed small areas of ulceration.

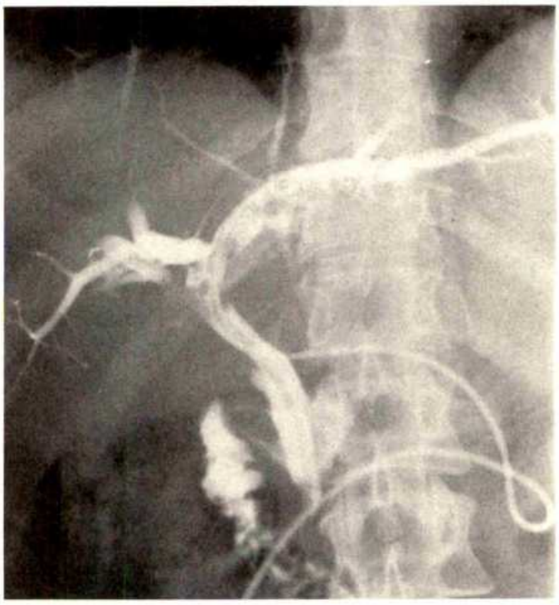

Figure 3 *Stricture of the common hepatic duct in a 25-year-old woman with a* T *tube in place (case 6)*

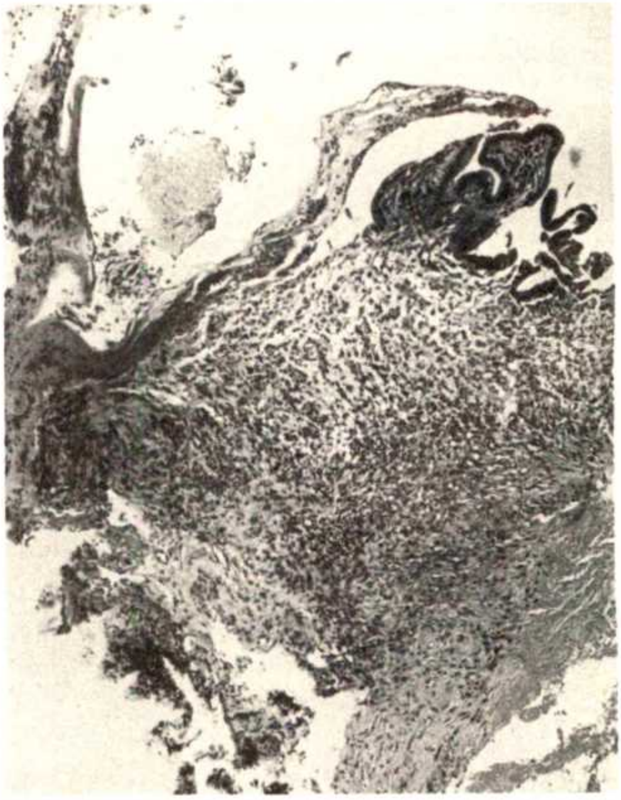

Figure 4 *Bile duct biopsy showing ulceration, hyperplastic epithelium and densely inflamed granulation tissue (original magnification × 90)*

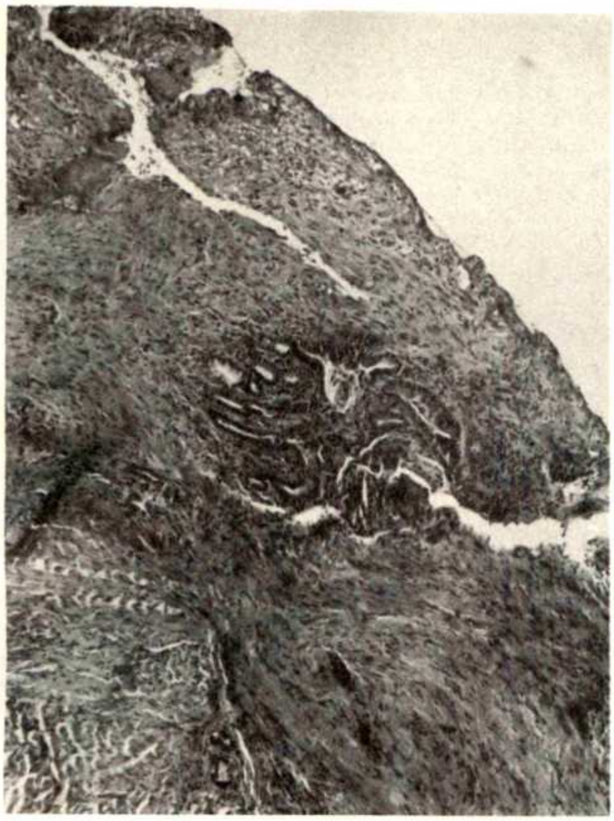

Figure 5 *Bile duct biopsy showing an island of hyperplastic epithelium surrounded by dense fibrous tissue (original magnification × 90)*

3. *Fibrosis and/or granulation tissue*: granulation tissue was commonly present immediately below the bile duct epithelium. Fibrosis was present in almost all biopsies and in all layers of the bile duct wall, sometimes accompanied by a myxoid ground substance. The fibrosis had obliterated much of the smooth muscle normally present in the walls of the extrahepatic bile ducts. Occasional spindle cells with eosinophilic cytoplasm and large, irregular and hyperchromatic nuclei were present in the stroma. These probably represent active fibroblasts or myofibroblasts.
4. *Changes in bile duct epithelium*: the epithelial changes took several forms. Epithelium adjacent to areas of ulceration showed some hyperplastic and regenerative features with enlarged, occasionally hyperchromatic, nuclei. Irregular glandular structures were present in some biopsies, either at the luminal surface or trapped within areas of fibrosis (*Figure 5*). In a few biopsies, the appearance of the glands, composed of cells with large, hyperchromatic and irregular nuclei, had been interpreted as suggestive of carcinoma.

Of these four main features (chronic inflammation, ulceration, fibrosis, and epithelial changes) at least three were present in each case. The mucosal ulceration in particular suggests that these strictures are caused by a process distinct from sclerosing cholangitis as the epithelium remains intact in that disease. The tissue response of fibroblastic proliferation rather than polymorphonuclear infiltration in the extrahepatic bile ducts is in keeping with a chemical rather than a bacterial cause for the inflammation. In some biopsies, the epithelial changes were suggestive of malignancy but the clinical course and, when taken, subsequent biopsies show these to be hyperplastic or regenerative.

Discussion

Benign, inflammatory, non-traumatic strictures of the extrahepatic bile ducts are extremely rare[7]. Primary sclerosing cholangitis is a rare disease characterized by chronic inflammatory fibrosis of the biliary tree with intact mucosa[8], usually affecting both the intrahepatic and extrahepatic ducts[1-8]. The diagnosis of primary sclerosing cholangitis rests on the cholangiographic demonstration of stricturing and beading of the biliary tree in the absence of other causes of ductal stenosis[2]. Primary sclerosing cholangitis is a disease of unknown aetiology, which must be distinguished in particular from cholangiocarcinoma, from which it may be very difficult to differentiate[9]. In patients who have primary sclerosing cholangitis affecting the extrahepatic biliary tree, cholangiography shows characteristically alternating areas of constriction and dilatation involving the entire bile duct[1-3]. However, it has been shown[7,10] that sclerosing cholangitis may affect only a segment of the extrahepatic ducts, mimicking a cholangiocarcinoma. Nevertheless, this possibility has been considered to be very infrequent, and according to Longmire *et al.*[11] most authors consider that any localized obstruction in the extrahepatic bile duct coexisting with dilatation of the intrahepatic radicles should be interpreted as cholangiocarcinoma until proved otherwise.

The radiological appearances are often interpreted as cholangiocarcinoma, possibly with extensive ductal involvement. Although the radiological appearance in the case reported by Panes *et al.*[12] suggested that sclerosis involved only a small segment of the common hepatic duct, the histological examination, as well as the surgical findings, indicated more extensive involvement of the extrahepatic biliary tree and this has also been recently observed by others[2,6]. Hadjis *et al.*[7] reported eight patients with isolated extrahepatic strictures and also suggested that they represented localized forms of sclerosing cholangitis.

The 12 cases presented here are all histologically proved examples of benign, inflammatory, non-traumatic stricturing of the extrahepatic bile ducts. All underwent preoperative cholangiography, laparotomy and biopsy and all have subsequently had long-term follow-up with no deaths. Several factors are of interest in this series. First, ten of the 12 were confidently diagnosed as malignant on radiological assessment. Secondly, the histological examination has shown mucosal ulceration, suggesting that the process of inflammation in these cases is not the same as in sclerosing cholangitis, where there is a non-specific diffuse fibrotic thickening of the bile duct wall with the mucosa remaining intact. The prognosis appears to be good after surgical bypass, whereas the treatment of sclerosing cholangitis is unsatisfactory and the prognosis poor, with recurrent acute cholangitis, cirrhosis and bleeding from varices[4]. In one series the mean duration in 11 patients from the onset of symptoms to death was 7 years[1], which compares with a mean follow-up period of 8·6 years in our patients. Six of our patients are now more than 10 years from diagnosis with no evidence of either sclerosing cholangitis or malignancy in the biliary tract. Thirdly, in several cases that were initially inoperable, tube intubation allowed relief of the jaundice and the inflammatory process subsequently resolved spontaneously (even after several years), allowing bypass with a Roux-en-Y loop of jejunum. Fourthly, it is of some concern that in previous publications that recommended stenting of biliary strictures[13] or irradiation of cholangiocarcinomas with iridium-192 wire[14] tissue for histological examination was not obtained in all cases. It is possible that some cases may have received inappropriate treatment.

In conclusion, we agree with previous authors[7] that biopsy tissue should be obtained whenever possible in cases of extrahepatic biliary strictures that present with dilatation of the intrahepatic ducts as radiology alone is often insufficient to make a firm diagnosis of malignancy. Intubation should not be considered permanent in cases with benign histology, and follow-up radiology with second laparotomy may be valuable as spontaneous regression of the inflammatory process can occur. The histological observations in this series suggest that benign strictures of the extrahepatic ducts may occur without evidence of sclerosing cholangitis, and the prognosis after surgical resection appears to be very satisfactory.

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Three-dimensional morphological study of the pancreatic microvasculature in caerulein-induced experimental pancreatitis

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A morphological study of the pancreatic microvasculature in experimental pancreatitis was performed in dogs, using three-dimensional scanning electron microscopy vascular casting and transmission electron microscopy. Animals with pancreatitis were characterized by a marked reduction in the number of capillaries outlined by the cast and by distortion of those that were outlined, with irregularity of the capillary lumen, abruptly terminating capillary buds and leakage of the cast material through the capillary membrane. The study provides convincing morphological evidence that one of the earliest changes in acute pancreatitis is distortion of the capillary circulation.

Keywords: Pancreas, blood supply, experimental pancreatitis, caerulein, electron microscopy

Perfusion studies of the isolated pancreatitis model suggest that one of the earliest changes in acute pancreatitis is an alteration in capillary permeability[1]. The aim of the present investigation was to perform a three-dimensional morphological study of the pancreatic microvasculature in an *in vivo* experimental model using a combination of scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

Materials and methods

Ten adult mongrel dogs were anaesthetized using 5 per cent chloralose in 25 per cent urethane ($1{\cdot}5\,\mathrm{ml\,kg^{-1}}$). Group A animals (five dogs) received a 2-h intravenous infusion of normal saline ($30\,\mathrm{ml\,h^{-1}}$) while group B animals (five dogs) received a 2-h infusion of caerulein ($10\,\mu\mathrm{g\,kg^{-1}\,h^{-1}}$ at $30\,\mathrm{ml\,h^{-1}}$). The caerulein was dissolved in 1:10 saline dilution of the dogs' own serum. Blood was removed for serum amylase determination before infusion, at 20-min intervals during infusion, and again at the end of the 2-h infusion period.

Laparotomy was then performed and all the minor vessels leading to the right lateral lobe of the pancreas were isolated and ligated. The inferior pancreaticoduodenal artery was cannulated using a 21 Fr cannula and the inferior pancreaticoduodenal vein was ligated. A ligature was then tied tightly around the medial portion of the right lobe, effectively isolating it from the body of the pancreas, and a single venous outlet was created by incising the main vein which courses along the dorsal surface of the gland at the medial aspect of the right lateral lobe. The right lobe was then perfused via the cannula, firstly with normal saline (20 ml) and then with 2·5 per cent glutaraldehyde (20 ml). Twenty minutes later the lobe was perfused with a low viscosity casting medium, Mercox® (20 ml) (Ladd Research Industries Incorporated, Burlington, Vermont, USA). The casting material was allowed to dry and harden for 20 min.

The casted pancreas was digested for 7–10 days in 34 per cent potassium hydroxide at 40°C. When digestion was complete, the cast was washed to neutrality, dried in air, coated with gold and examined using SEM.

Specimens of the fixed pancreas perfused with saline and glutaraldehyde alone were prepared for TEM using standard methods[2]. Sections were stained with uranyl acetate and lead citrate and examined in a JEOL 2000 EX® (Japanese Electron Optics Ltd., Tokyo, Japan) electron microscope. Semi-thin sections were stained with toluidine blue for light microscopy.

Results

Pancreatitis was induced in all five group B animals, as evidenced by a significant rise in serum amylase levels (*Figure 1*), histological examination (*Figure 2*) and gross appearances at laparotomy (the gland was inflamed and oedematous with clear delineation of individual lobules by the oedema).

SEM studies of casts of the normal and inflamed pancreas are compared in *Figures 3–5*. Pancreatitis specimens were characterized by a gross reduction in the number of capillaries outlined by the cast (*Figure 3*). Those that were outlined were irregular, and several ended abruptly in smoothly tapered ends (*Figure 4*). Blebs of cast were visible along the capillary surface, suggesting leakage of casting material through the capillary wall (*Figure 5*).

The findings on SEM were supported by cross-sectional TEM views of the capillary lumen: the group of animals with pancreatitis was characterized by irregularity of the endothelial capillary lining (*Figure 6*).

Discussion

Caerulein is an analogue of cholecystokinin, a known stimulant of pancreatic exocrine secretion, and when it is administered

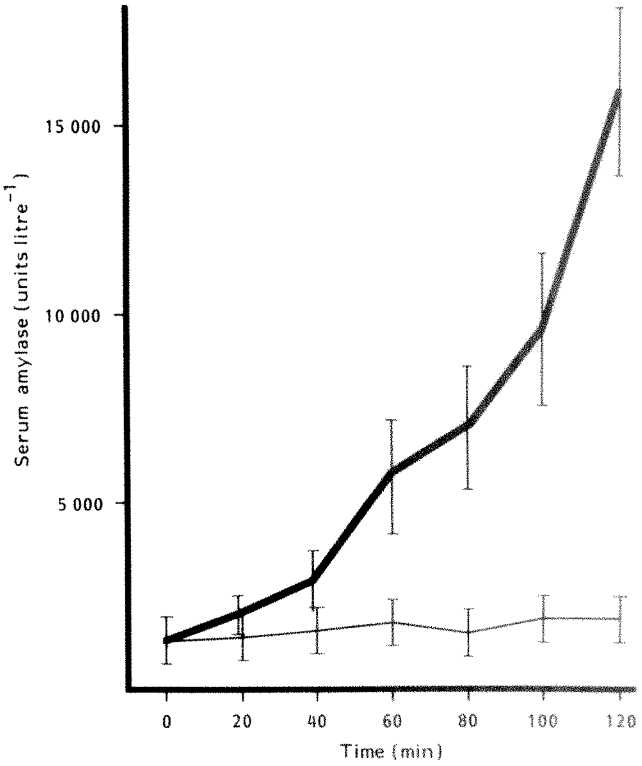

Figure 1 *Serum amylase response to saline (——) and caerulein (——) infusion in dogs. Each point represents mean(s.d.); n = 5*

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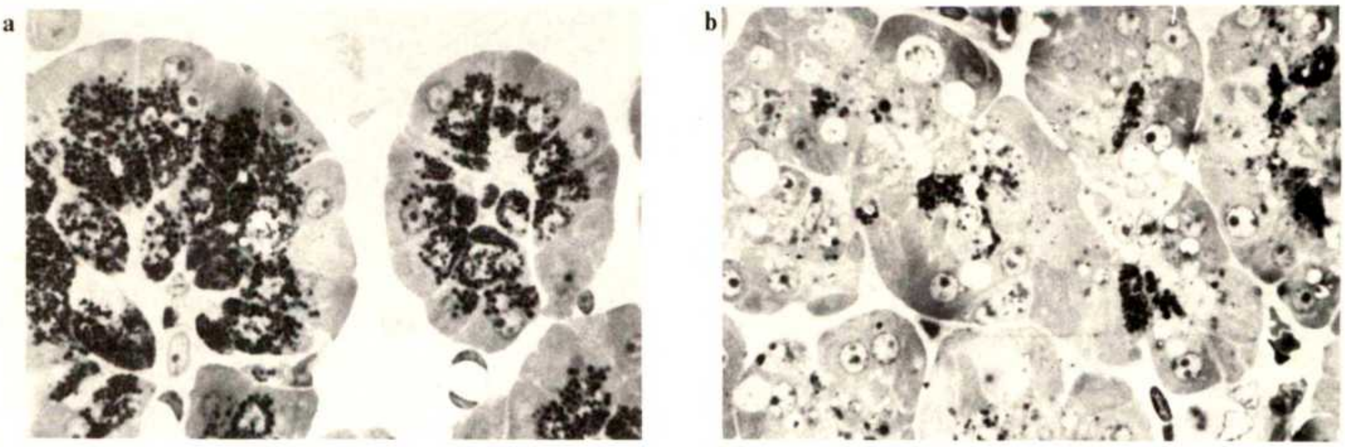

Figure 2 *Light microscopic photomicrographs of dog pancreas after* **a** *saline and* **b** *caerulein infusion, showing loss of zymogen granules and development of numerous intracytoplasmic vacuoles. These micrographs were stained with toluidine blue. (Original magnification* × 4500)

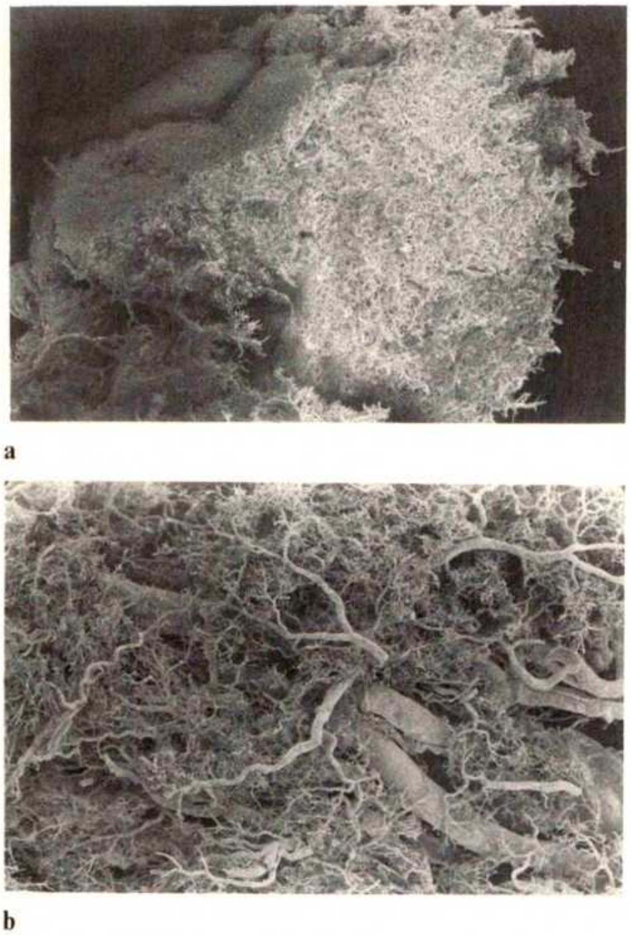

Figure 3 *Scanning electron photomicrographs of the dog pancreas after* **a** *saline and* **b** *caerulein infusion, showing a gross reduction in the number of capillaries outlined by the cast in the animals with pancreatitis. (Original magnification* × 15)

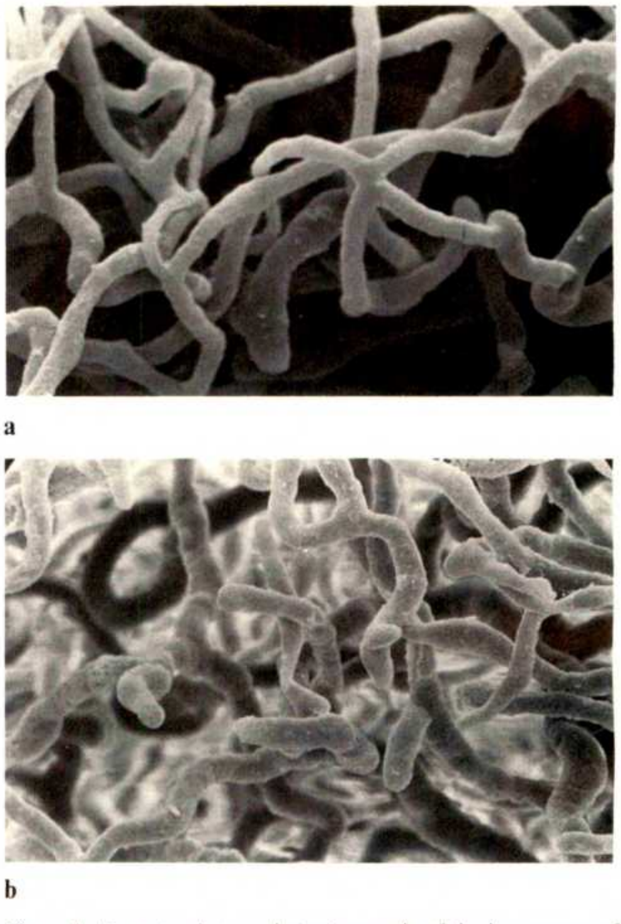

Figure 4 *Scanning electron photomicrographs of the dog pancreas after* **a** *saline and* **b** *caerulein infusion, showing an irregular arrangement of the capillaries with some smoothly tapered ends in the animals with pancreatitis. (Original magnification* × 1000)

in supramaximal doses, as it was in this study, it induces an interstitial oedematous pancreatitis[3]. The caerulein model has been widely used in the rat[3–6] but reports in the literature of the use of the canine model are rare[7,8]. In the present study, histological examination confirmed that the pancreatitis was oedematous in nature, similar to that reported in the rat[5]. Acute necrotizing pancreatitis has been described in dogs using a caerulein infusion model[7], but in that case histological examination was carried out 12 h rather than 2 h after commencement of the infusion.

The pancreatic microcirculation in pancreatitis has been previously investigated using angiography and light microscopic examination of vascular casts. Some of the features reported above have been described[9–11], but the combination of SEM and TEM provides a more detailed and more accurate three-dimensional study[12]. Abruptly terminating small arteries have been reported using light microscopy[10] but analysis using SEM and TEM in this study confirms that these abruptly terminating vessels are capillaries, which may explain the gross reduction in the extent of capillaries outlined by the cast in pancreatitis. Why the vascular casts should terminate so abruptly is unclear. There was no evidence of intravascular thrombosis found on cross-sectional examination by TEM.

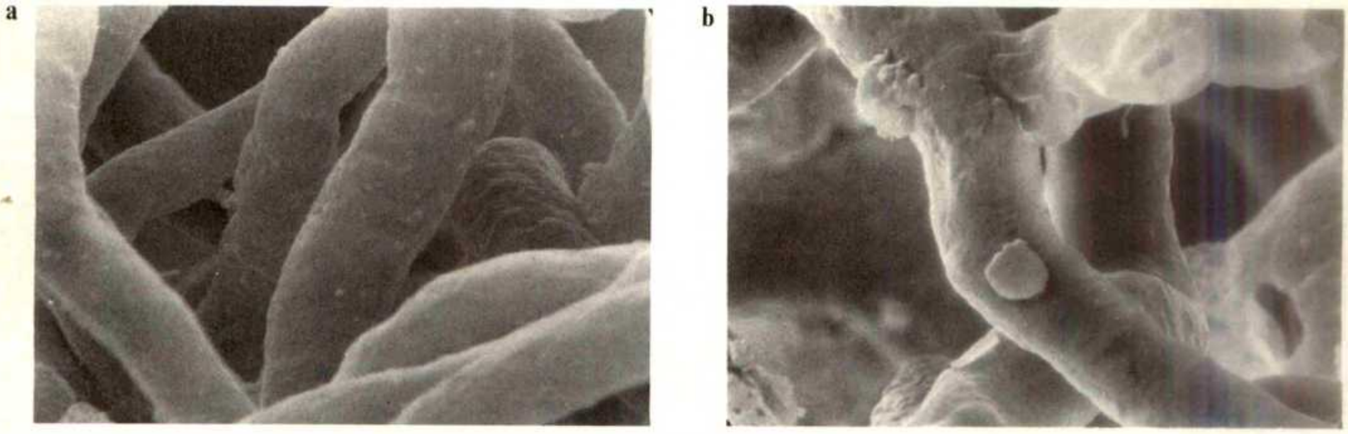

Figure 5 *Scanning electron photomicrographs of the dog pancreas after* **a** *saline and* **b** *caerulein infusion, showing blebs of cast on the capillary surface in animals with pancreatitis, suggesting leakage through the capillary wall. (Original magnification* × *3000)*

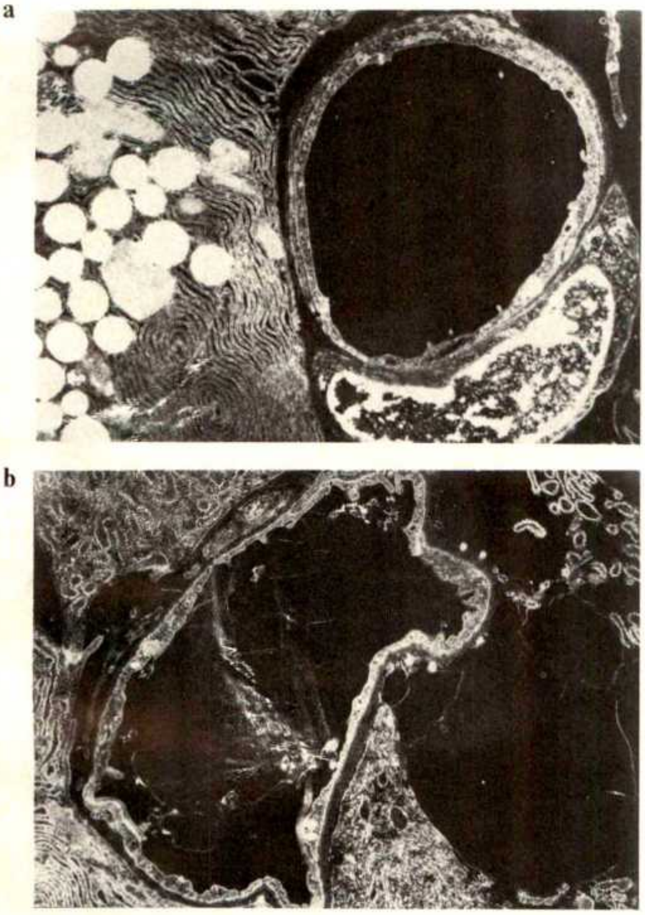

Figure 6 *Transmission electron photomicrographs after* **a** *saline and* **b** *caerulein infusion, showing irregularity of the endothelial capillary lining in animals with pancreatitis. (Original magnification* × *12 000)*

Precapillary sphincters have been identified in the cat pancreas[11] and the possibility of such sphincters in the dog is supported by evidence of local arteriovenous shunting in other canine pancreatitis models[10,13]. Such sphincters could explain the paradoxical findings in the caerulein model of an increase in pancreatic blood flow[9] despite a reduction in the number of perfused capillaries; perhaps the abruptly terminating capillary casts are the result of impaired flow due to sphincter spasm.

The irregular outline of the capillary casts in this and other studies[10,11] has been attributed to external compression of the capillaries by oedema but the findings on TEM in this study strongly suggest that the irregularity is due to disruption of the capillary endothelial lining, which could in turn explain the altered capillary permeability reported to occur early in the disease process[1].

The combination of longitudinal SEM views of casts of the vascular tree and cross-sectional TEM views of the vascular lumen provides an ideal technique for a detailed three-dimensional study of the visceral microcirculation. The technique demonstrated early distortion of the local microcirculation in the development of pancreatitis; further studies are underway to assess the time factor involved in these changes and to evaluate the microcirculation in the pancreas and other organs known to be impaired in this and other established models of pancreatitis.

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Endoscopic sphincterotomy for bile duct stones in patients with intact gallbladders

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Endoscopic sphincterotomy was performed in 121 patients (age range 34–92 years; median 80 years) with intact gallbladders and bile duct stones. Clearance of the duct by basket or balloon extraction was attempted in 97 patients (80 per cent) and achieved in 93 of these patients (96 per cent). In 24 patients the duct was left to empty spontaneously and this occurred in 22 patients. Immediate complications due to endoscopic sphincterotomy occurred in five patients (two haemorrhage, two perforation, one haemorrhage and perforation). Of the 101 patients reviewed 12–72 months (median 24 months) after endoscopic sphincterotomy, 76 (75 per cent) have remained asymptomatic throughout the follow-up period. Eighteen patients (18 per cent) required cholecystectomy for recurrent gallbladder symptoms 1–24 months after endoscopic sphincterotomy. One of the asymptomatic patients underwent cholecystectomy on the advice of his consultant. A further seven had recurrent biliary colic or cholangitis necessitating enlargement of the sphincterotomy and further stone retrieval in three of these patients. Endoscopic sphincterotomy is an effective treatment for bile duct stones in high risk patients, but subsequent cholecystectomy is required in a significant number of patients owing to continuing gallbladder symptoms.

Keywords: Common bile duct, endoscopic sphincterotomy

The use of endoscopic sphincterotomy to remove bile duct stones is increasing rapidly, especially in elderly, infirm patients. While this technique avoids surgery in the short term, remaining cholelithiasis can cause biliary colic, acute or chronic cholecystitis, and even jaundice. If these symptoms are severe or persistent, cholecystectomy may be necessary. It has been suggested recently, however, that surgery will be required only rarely provided the bile duct is cleared at the time of endoscopic sphincterotomy[1]. The aim of this study was to assess the natural history of patients with cholelithiasis following endoscopic sphincterotomy for choledocholithiasis, with particular reference to the need for subsequent cholecystectomy.

Patients and methods

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy were performed in 121 patients with intact gallbladders and bile duct stones. Seven of these patients required a second ERCP to achieve adequate sphincterotomy. Many of the patients were referred specifically for ERCP from other hospitals in the west of Scotland. All patients were seen by one or more of the surgical authors soon after admission, and in view of age and general fitness it was decided to adopt non-surgical management in the first instance. The 52 men and 69 women patients had a median age of 80 years, ranging from 34 to 92 years. The 34-year-old was a grossly obese woman who presented with deep jaundice and markedly disordered liver function tests. Eighty-three per cent of patients were aged 70 years or more and 55 per cent were aged 80 or more. The main presenting features were jaundice in 70 patients, cholangitis in 22, pain in 19 and acute pancreatitis in seven. Three elderly patients presented with vague confusion states and were found to have upset liver function tests. Many patients had a combination of signs and symptoms. No patient exhibited clinical features suggestive of significant gallbladder inflammation at the time of sphincterotomy. Significant cardiovascular disease was present in 48 patients and obesity in 14 patients. Other coexisting illnesses included cerebrovascular disease, diabetes mellitis, multiple sclerosis, connective tissue disorders and abdominal aortic aneurysm.

ERCP and endoscopic sphincterotomy were performed under intravenous sedation and antibiotic cover when appropriate. The Olympus JF1T 10 duodenoscope (KeyMed, Southend-on-sea, UK) and a sphincterotome attached to adiathermy unit were used. An active policy of bile duct clearance following sphincterotomy was not adopted routinely, but attempts were made to remove stones greater than 1 cm in diameter using a Dormia basket or a balloon catheter. In the event of failure to clear the duct in such circumstances, repeat ERCP was performed during the same admission, usually within 1 week. In a small number of patients with large bile duct stones (1–2 cm), nasobiliary catheter drainage was established before either stone extraction or methyl tertiary butyl ether (MTBE) stone dissolution. If the duct contained only small stones, these were left to pass spontaneously, in which case a repeat ERCP was performed 4–6 weeks later, or immediately in the event of further symptoms. Patients were reviewed at a surgical outpatient clinic.

Results

The outcome of the 121 patients who underwent endoscopic sphincterotomy is summarized in *Figure 1*.

Stone retrieval (Table 1)

Of the 93 patients whose ducts were cleared during the first admission, this was achieved at the first attempt in 57 patients. A further ERCP during the same admission in the remaining 36 patients revealed spontaneous duct clearance in 12, while in 18 patients the duct was cleared subsequently using a Dormia basket. Six patients with large stones required nasobiliary catheter insertion followed by MTBE stone dissolution therapy and/or stone extraction. Three patients had large stones which could not be caught by the basket, and they required surgical clearance of the duct. One further patient required surgery to remove the Dormia basket which became impacted in the bile duct after snaring a large stone. Twenty-two of 24 patients in whom duct clearance at the time of endoscopic sphincterotomy was not attempted had clear ducts at review ERCP 4–6 weeks later. Overall, of the 117 patients whose ducts were cleared endoscopically, 91 required one ERCP examination, 23 required two, and three required three ERCPs to empty the duct.

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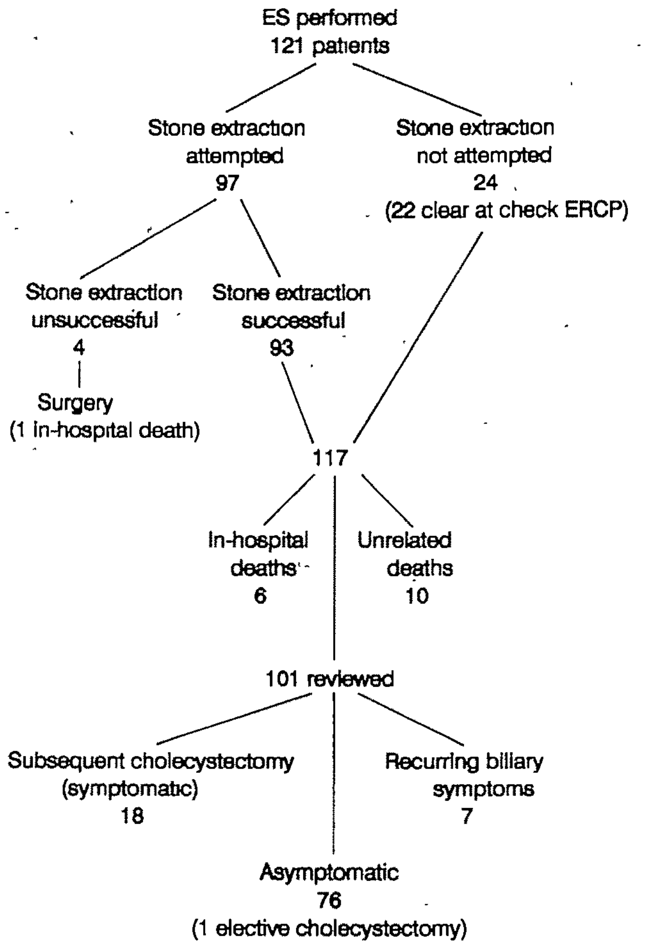
ES performed
121 patients
Stone extraction attempted
97
Stone extraction not attempted
24
(22 clear at check ERCP)
Stone extraction unsuccessful
4
Surgery
(1 in-hospital death)
Stone extraction successful
93
117
In-hospital deaths
6
Unrelated deaths
10
101 reviewed
Subsequent cholecystectomy (symptomatic)
18
Recurring biliary symptoms
7
Asymptomatic
76
(1 elective cholecystectomy)

Figure 1 *Outcome of 121 patients undergoing endoscopic sphincterotomy (ES) for bile duct stones; ERCP, endoscopic retrograde cholangiopancreatography*

Table 1 *Stone retrieval following endoscopic sphincterotomy*

	Number of patients
ERCP and ES ($n=121$)	
Duct clearance achieved during first admission	93 (76·9%)
Failed attempt to clear duct	4 (3·3%)
Stones left to pass spontaneously	24 (19·8%)
Bile duct confirmed as empty at check ERCP	(22)
Stones remaining but cleared at check ERCP	(2)

ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy

Complications (Table 2)

Three patients suffered retroperitoneal perforation at endoscopic sphincterotomy, were treated conservatively, and survived. Of the three patients with haemorrhage following endoscopic sphincterotomy, one required emergency surgery and subsequently died. At follow-up the bile duct was clear in the four surviving patients who had sustained perforation and/or haemorrhage. Three of the six patients with cholangitis had this before endoscopic sphincterotomy, while four of the nine patients with acute symptomatic pancreatitis had pancreatitis before endoscopic sphincterotomy. Asymptomatic hyperamylasaemia (range 312–5290 units/l) occurred in 30 (25 per cent) patients.

Of the six patients with cholangitis four subsequently died. One of these patients, who required a wide endoscopic sphincterotomy for a large stone and pus in the bile duct showed evidence of continuing biliary sepsis and required laparotomy 6 days later. The principle cause of sepsis was found to be empyema, and the bile duct was noted to be empty of stones. Cholecystostomy was performed but the patient died of a myocardial infarction 24 h later. One patient whose bile duct was partially cleared at initial endoscopic sphincterotomy underwent repeat ERCP for features of continuing cholangitis, but was confirmed at this examination to have an empty bile duct. This patient died 1 month later from bronchopneumonia. Two patients had a wide endoscopic sphincterotomy performed in the presence of tiny bile duct stones, where nasobiliary drainage was not thought to be necessary. Despite apparent free bile drainage one patient died 5 days and the other 8 days after endoscopic sphincterotomy from presumed continuing cholangitis. Five of the nine patients with acute pancreatitis had the bile duct cleared at the first attempt. The pancreatic duct was outlined in eight of these patients.

There were seven in-hospital deaths occurring up to 36 days after endoscopic sphincterotomy. In addition to the patient who required surgery for haemorrhage and the four patients discussed above, the patient who required surgery for removal of the impacted Dormia basket died of respiratory failure. A further patient died of pancreatitis, which had been the presenting complaint before endoscopic sphincterotomy.

Follow-up

Of the 121 patients who entered the study, ten patients died of unrelated diseases. Four patients required early surgery for large bile duct stones during their initial admission. One of these patients and six others died during their initial hospital stay. Thus, 101 patients were available for review in a median follow-up of 24 months (range 12–70 months).

Seventy-six patients had remained asymptomatic throughout the follow-up period, while 25 had experienced further biliary tract symptoms. Eighteen of these 25 patients, plus one asymptomatic patient, underwent cholecystectomy 1–24 months after sphincterotomy.The reasons for surgery are shown in *Table 3.* Of the seven patients who came to surgery because of recurring episodes of cholecystitis, five required urgent laparotomy for empyema of the gallbladder. Initial surgery in one of these patients was limited to cholecystectomy. In 11 of the 25 patients, the bile duct had not been cleared, yet at the time of cholecystectomy operative cholangiography revealed

Table 2 *Complications of endoscopic retrograde cholangiopancreatograpy and endoscopic sphincterotomy*

Complication	Number of patients
Retroperitoneal perforation	3 (2·5)*
Haemorrhage from ES site	3 (2·5)*
Cholangitis	6 (4·9)
Acute symptomatic pancreatitis	9 (7·4)

* These six complications occurred in five patients, with one patient having both perforation and haemorrhage, ES, endoscopic sphincterotomy

Table 3 *Reasons for cholecystectomy*

	Number of patients	Number of patients with stones in gallbladder	Number of patients with stones in bile duct
Biliary colic	10	9	2
Cholecystitis/empyema	7	7	—
Recurring biliary colic and jaundice	1	1	1
Consultant decision*	1	1	1

* Asymptomatic patient; none of the four patients with bile duct stones underwent surgery because of symptoms primarily relating to the presence of duct stones

bile duct stones in only four patients. One of the patients operated on for recurring biliary colic had no stones in the gallbladder by the time of cholecystectomy but had one stone in the bile duct, while another patient had stones both in the gallbladder and bile duct. In both these cases, the duct had been cleared of stones at the time of endoscopic sphincterotomy. One patient underwent surgery on the advice of the consultant in charge because of cholelithiasis but had been asymptomatic. Despite complete duct clearance, this patient was shown at cholecystectomy to have a further bile duct stone.

Seven patients have had recurring biliary symptoms but, as yet, have not required cholecystectomy. Four of these patients have had recurring episodes of biliary colic. This settled spontaneously in two patients but the other two required enlargement of the sphincterotomy to remove further bile duct stones. These four patients had clear ducts following initial endoscopic sphincterotomy. Three patients have had recurring attacks of cholangitis, necessitating repeat ERCP and duct clearance. Two of these patients died shortly after this review, one of peptic ulcer haemorrhage and the other of persisting cholangitis. This latter patient had been admitted to another unit where it had been decided that further intervention was inappropriate. Post-mortem examination confirmed the presence of a further stone within the bile duct

Discussion

Endoscopic sphincterotomy is an effective treatment for symptomatic bile duct stones in high risk patients, although the procedure is not free of complications. The immediate complications and mortality rate in the present series compare favourably with other reported studies[2–4]. In a recent study of 114 patients with intact gallbladders, Neoptolemos *et al.*[5] reported 22 major complications and nine deaths following endoscopic sphincterotomy. These authors suggested that the mortality rate may be reduced by improved management of complications. Haemorrhage following sphincterotomy can be rapid and fatal, or may be manifested only by a fall in haemoglobin concentration. When haemorrhage is severe enough to warrant operative intervention, survival is rare[1,6]. Complication and mortality rates must be viewed in the light of the patient population involved. Usually, sphincterotomy is performed because the patient is deemed an unacceptable surgical risk; therefore, if surgery becomes necessary due to a complication or failure of the technique, the outcome is inevitably poor. Thus, if sphincterotomy fails to clear the bile duct of large stones, alternative management such as the insertion of nasobiliary catheters followed by stone dissolution[7] or the use of endoprostheses[8] should be considered. Further possibilities such as extracorporeal shock wave lithotripsy remain to be evaluated.

This study demonstrates that although endoscopic sphincterotomy is an effective treatment, subsequent cholecystectomy is required in 18 per cent of patients due to continuing gallbladder symptoms. This conclusion differs from the findings of Martin and Tweedle[1], who suggested that cholecystectomy was not required provided the bile duct was cleared. In the present study, no routine attempt was made to clear the bile duct of small stones unless cholangitis was present. In the majority, the duct was clear when ERCP was repeated 4–6 weeks later. Furthermore, there was no correlation between duct non-clearance and the need for subsequent cholecystectomy.

It would be of value to be able to predict those patients who will require subsequent cholecystectomy. It has been suggested that if the gallbladder does not fill at ERCP, indicating probable cystic duct obstruction, then cholecystectomy is likely to be required[9,10], but this suggestion has not been supported by other series[1,11]. Indeed, in the present study filling of the gallbladder occurred in seven of the 18 patients who required subsequent cholecystectomy Furthermore, among the 83 patients who have not required cholecystectomy, no gallbladder filling occurred in 61. Indeed, of the 22 patients in whom gallbladder filling was seen, two have had recurring biliary symptoms. The presence of pre-existing cholangitis has been said to indicate likely gallbladder complications at a later date[11], but in the present series only six of the 18 patients who subsequently required cholecystectomy presented with cholangitis. Several patients in this series with gallbladders *in situ* illustrate that ducts initially cleared by endoscopic sphincterotomy may later show evidence of stones after further gallbladder colic.

In conclusion, while endoscopic sphincterotomy is an effective tretment for choledocholithiasis in this group of high risk patients, subsequent cholecystectomy was required in 18 per cent of patients due to recurring gallbladder symptoms. As the minimum follow-up of this group is currently 1 year, and because some of the patients who required cholecystectomy did so in the second year of follow-up, it is possible that more of these patients may require surgery as the study progresses

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Pancreatic duct pressure, duct permeability and acute pancreatitis

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The relationship between pancreatic duct pressure, duct permeability to macromolecules and the development of acute pancreatitis was studied in a cat model. Perfusion of the pancreatic duct with 15 mM glycodeoxycholic acid, ethanol administration, or secretagogue-stimulated pancreatic secretion against >50 per cent duct obstruction resulted in an increase in peak pancreatic duct pressure in all animals. Duct permeability to 20 000 molecular weight dextran molecules was increased in 22 of 29 experimental animals compared with two of 22 control animals ($P<0{\cdot}01$)*. Perfusion of the pancreatic duct with activated pancreatic enzymes resulted in acute pancreatitis in 24 of 29 experimental animals compared with three of 22 control animals* ($P<0{\cdot}01$)*. These results suggest that pancreatic ductal hypertension, resulting in increased ductal permeability to large molecules, may be a common early event in gallstone and alcoholic pancreatitis.*

Keywords: Alcohol, pancreatic duct, pressure, duct permeability, acute pancreatitis

Under normal circumstances pancreatic proenzymes are secreted into the pancreatic duct and are activated in the duodenum by the enzyme enterokinase. Premature activation of these proenzymes within the pancreas is thought to be an important early event in the pathogenesis of acute pancreatitis. The mechanism by which activated pancreatic enzymes gain access to the pancreatic parenchyma is unknown. Previous work from our laboratory suggests that under certain circumstances the cat pancreatic duct becomes permeable to molecules the size of pancreatic enzymes[1,2]. In those experiments, ductal perfusion with a bile salt or the oral administration of alcohol led to an increase in duct permeability to large molecular weight dextran molecules. When the duct was subsequently perfused with activated pancreatic enzymes, acute pancreatitis resulted. Perfusion of a non-permeable duct with active enzymes or perfusion of a permeable duct with inactive enzymes resulted in little or no histological damage to the pancreas. Pancreatic duct obstruction has also been implicated in the pathogenesis of acute pancreatitis. In these experiments we examined the relationship between pancreatic duct pressure, duct permeability and the development of acute pancreatitis in three models of the disease.

Materials and methods

Mongrel cats were anaesthetized with intramuscular xylazine (1 mg/kg) and intraperitoneal sodium pentobarbitone (25 mg/kg). A femoral vein was cannulated for the administration of fluid and drugs. Through a midline laparotomy incision the pancreas was exposed throughout its length. Three different experimental systems were used.

Experiment 1

In this experiment the effect of bile salt perfusion of the pancreatic duct on pancreatic duct pressure, duct permeability and the development of pancreatitis were studied. The pancreatic duct was cannulated in the head and tail of the gland using fine polyethylene tubing (*Figure 1*). Pancreatic duct pressure was measured via a pressure transducer connected to the cannula in the tail of the gland. The duct was perfused with a standard perfusate containing (HCO_3^-) 120, (Cl^-) 30, (Na^+) 150 mmol/l, pH 8·4 and osmolality 315 mosmol/l at 0·5 ml/h for 30 min to stabilize the system. Then the duct was perfused with either standard perfusate or 15 mM sodium glycodeoxycholate at the same rate of perfusion for 1 h. Pancreatic duct pressure was measured continuously throughout the perfusion period. Ductal permeability was assessed by measuring the recovery of 20 000 molecular weight fluoresceinated dextrans in portal venous blood following their perfusion along the pancreatic duct. The design of the system was such that if dextrans were recovered in portal venous blood they could only have got there by traversing the ductal system.

In a separate group of cats the pancreatic duct was cannulated in the tail of the gland. The duct was perfused with standard perfusate or sodium glycodeoxycholate as before and then perfused with pancreatic enzymes for 1 h at 0·5 ml/h. These enzymes were obtained from separate donor cats by collecting secretin/cholecystokinin-stimulated pancreatic juice and standardized to an amylase concentration of 35 units/ml. The enzymes in this juice were activated by *in vitro* incubation with porcine enterokinase. The cannulae were removed and the cannulation sites ligated. The abdomen was closed and the animals allowed to recover. The pancreas was examined for the presence of oedema and haemorrhage 24 h later and samples of the pancreas were excised for histological examination. Coded slides from each animal were examined by two independent observers for the presence of oedema, inflammatory cell infiltration and parenchymal necrosis. An 'inflammatory score' of 0–4 (with 4 representing the most severe changes) was given for each parameter and a total score of 0–12 derived by addition.

Experiment 2

In this experiment the effect of ethanol was studied. The pancreatic duct was cannulated in the tail of the gland as before and the duct perfused with standard perfusate for 30 min. The stomach was cannulated and the cats received either 20 ml of normal saline or 20 ml 40 per cent ethanol intragastrically over a 10-min period (*Figure 2*). Pancreatic duct pressure was measured continuously for 1 h during which the duct was perfused with standard perfusate at 0·5 ml/h. Serum ethanol levels were measured 1 h after ethanol instillation. Duct permeability was measured as before. In a separate group of cats the pancreatic duct was perfused with activated pancreatic enzymes 1 h after saline or ethanol administration and samples of the pancreas examined 24 h later.

Experiment 3

In this experiment the effect of pancreatic duct obstruction was studied. The pancreatic duct was cannulated in the tail of the gland as before. The duct in the head of the gland was isolated and 0, 25, 50, 75 or 100 per cent of its luminal diameter was obstructed with a microvascular clip, using a dissecting microscope to aid the placement (*Figure 3*). The gland was stimulated to secrete by an intravenous bolus injection of secretin (2·0 units/kg) and cholecystokinin octapeptide (0·08 μg/kg) and the pancreatic duct pressure was measured continuously for 1 h. Then the obstructing clip was removed, duct permeability was measured and the duct was perfused with activated pancreatic enzymes as before.

This paper was presented at the Meeting of the Surgical Research Society which took place in Bristol, UK, in July 1988.

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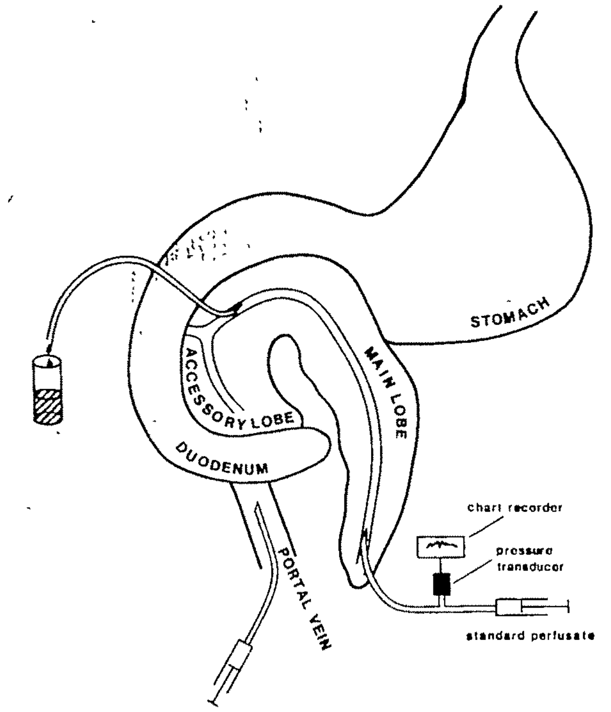

Figure 1 *Diagrammatic representation of the model used to study the effect of sodium glycodeoxycholate on pancreatic duct pressure, duct permeability and the development of acute pancreatitis. Normal saline or sodium glycodeoxycholate was perfused through the duct via the cannula in the tail of the gland and ductal pressure measured via the transducer connected to this cannula Large molecular weight fluoresceinated dextrans were perfused along the duct and portal venous blood was sampled for its dextran content via a cannula placed in the portal vein just distal to its origin from the superior mesenteric and splenic veins Then, in a separate group of cats, activated pancreatic enzymes were perfused along the duct*

The results were analysed using Fisher's exact test for nominal data and the Mann–Whitney *U* test for ordinal data. Statistical significance was assumed where $P < 0.05$.

Results

Perfusion of the pancreatic duct with sodium glycodeoxycholate, intragastric instillation of ethanol and pancreatic secretion against ductal obstruction of 50 per cent or greater all led to a significant increase in pancreatic duct pressure (*Table 1*). In experiments 1 and 3 the pressure rise was seen within a few minutes of introducing sodium glycodeoxycholate or secretagogue and reached a peak by 10 min. In each group the pressure then gradually fell to a plateau level above basal pancreatic duct pressure which was sustained throughout the hour of pressure measurement. In experiment 2 the pressure rise occurred within 10 min of ethanol instillation into the stomach and was sustained throughout the hour of pressure measurement. Mean(s.e.m.) serum ethanol levels 1 h after ethanol administration were 258(24) mg/dl.

Overall, ductal permeability to 20 000 molecular weight dextran molecules was increased in 22 of 29 experimental animals compared with only two of 22 control animals ($P < 0.01$; *Table 1*). When activated pancreatic enzymes were perfused along the pancreatic duct, acute pancreatitis developed within 24 h in 24 of 29 experimental animals compared with only three of 22 control animals ($P < 0.01$). In most cases the pancreas showed changes of oedematous pancreatitis but some animals in the secretion against obstruction group developed haemorrhagic pancreatitis. The inflammatory scores were significantly higher in each experimental group compared with the respective control group (*Table 2*).

Discussion

Reflux of bile into the pancreatic duct, alcohol ingestion and secretion against pancreatic duct obstruction have all been implicated in the pathogenesis of acute pancreatitis. The experiments described in this paper were designed to simulate

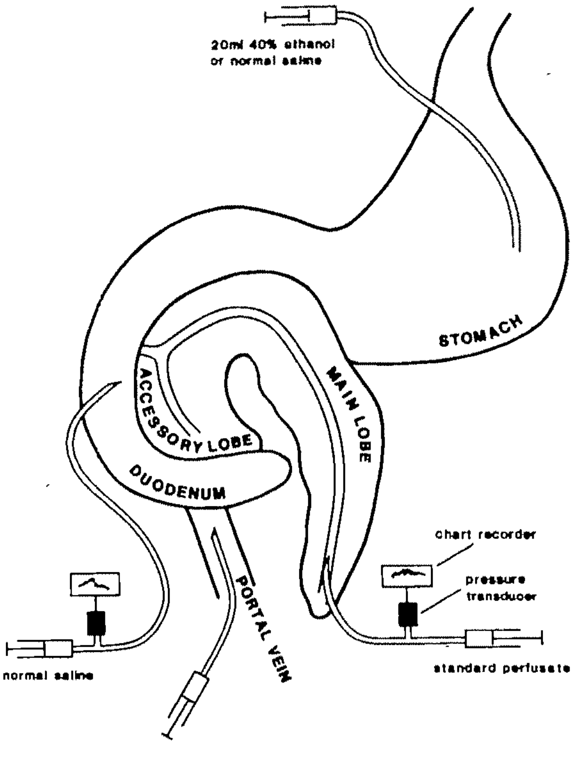

Figure 2 *Diagrammatic representation of the model used to study the effect of alcohol Ethanol or saline was instilled into the stomach as shown Intraduodenal pressure was also measured in all animals and remained constant throughout the procedure*

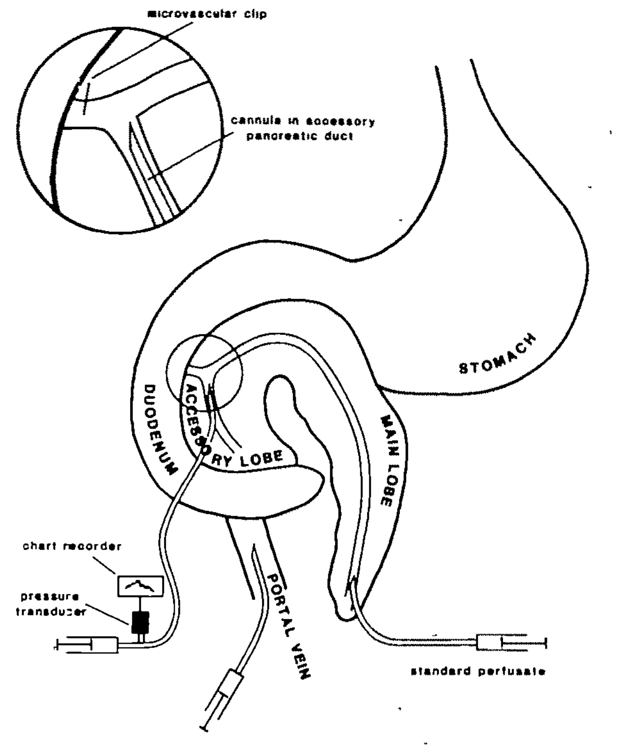

Figure 3 *Diagrammatic representation of the model used to study the effect of pancreatic duct obstruction. The microvascular clip (shown in the insert) was placed with the aid of a dissecting microscope and its position was confirmed by a second observer*

Table 1 *The effect of sodium glycodeoxycholate, ethanol and ductal obstruction on pancreatic duct pressure and duct permeability*

Group	Mean (s.e.m.) peak pancreatic duct pressure (mmHg)	Cats with permeable ducts‡
Standard perfusate perfusion	8·7 (0·6)	0/6
Sodium glycodeoxycholate perfusion	22·1 (4·7)*	5/6†
Intragastric saline	8·7 (0·4)	0/6
Intragastric ethanol	14·5 (1·3)*	5/6†
Obstruction (%)		
0–25	12·8 (2·0)	2/10
50–100	23·2 (1·7)*	12/17†

* $P<0·01$, Mann–Whitney *U* test; † $P<0·01$, Fisher's exact test; ‡ in these cats dextran molecules were recovered from portal venous blood following their perfusion along the pancreatic duct

Table 2 *The effect of sodium glycodeoxycholate, ethanol and ductal obstruction on the development of acute pancreatitis*

Group	Cats with pancreatitis	Inflammatory score mean (s.e.m.)
Standard perfusate perfusion	0/6	3·2 (0·3)
Sodium glycodeoxycholate perfusion	6/6†	9·6 (0·9)*
Intragastric saline	1/6	3·8 (1·0)
Intragastric ethanol	6/6†	7·1 (0·9)*
Obstruction (%)		
0–25	2/10	5·5 (0·6)
50–100	12/17†	7·9 (0·6)*

* $P<0·01$, Mann–Whitney *U* test; † $P<0·01$, Fisher's exact test

these events in a cat model. Thus, bile reflux was simulated by ductal perfusion with a bile salt at a concentration similar to that seen in human gallbladder bile[3]. Ethanol administration was simulated by intragastric instillation of ethanol resulting in similar serum concentrations found after acute alcohol intoxication in man[4]. Pancreatic secretion against partial or complete pancreatic duct obstruction, caused by gallstone impaction at the ampulla of Vater, was simulated by means of secretion against an obstructing microvascular clip. All of these events led to an increase in pancreatic duct pressure and an increase in ductal permeability to large molecules. The mechanism underlying ductal hypertension following duct obstruction with active pancreatic secretion is obvious. However, the mechanism by which pancreatic duct pressure rises following ductal perfusion with sodium glycodeoxycholate or intragastric ethanol administration is less clear. Most studies of the effect of ethanol on the sphincter of Oddi have shown an increase in sphincteric tone[5–9] and this, coupled with an increase in pancreatic secretion following ethanol, might lead to an increase in ductal pressure. The effect of sodium glycodeoxycholate on ductal pressure cannot be explained as easily because the sphincter of Oddi was excluded from the system in experiment 1 by placing a cannula in the pancreatic duct proximal to the sphincter. It is possible that the pressure increase seen with sodium glycodeoxycholate perfusion was due to partial duct obstruction by cellular debris shed from the luminal cells as a result of the detergent action of the bile salt, or alternatively by ductal spasm.

In all three models an increase in pancreatic duct permeability to large molecules was seen following the pancreatic duct insult. The mechanism by which the cat pancreatic duct becomes permeable to large molecular weight molecules is uncertain. The effects of sodium glycodeoxycholate, ethanol and pancreatic duct obstruction on pancreatic duct pressure suggest that ductal hypertension may be a common factor leading to the increase in ductal permeability.

Dextran molecules of molecular weight 20 000 were used as the markers of duct permeability as their size approximates that of several pancreatic enzymes including trypsin (23 000), chymotrypsin (25 000) and phospholipase A (14 000). Previous work has shown that the dextran molecules are not physically or chemically altered when they cross the pancreatic duct and vascular barriers[10]. When activated pancreatic enzymes were perfused along a permeable pancreatic duct, acute pancreatitis resulted in the majority of animals. This suggests, but does not prove, that pancreatic enzymes escaped from the duct into the surrounding parenchyma and initiated events leading to the development of acute pancreatitis. It is important to point out that in these experiments activated pancreatic enzymes were artificially introduced into the permeable pancreatic duct. We have also previously shown that the presence of inactive enzymes within a permeable duct does not lead to acute pancreatitis. However, there is evidence that under certain circumstances activated pancreatic enzymes can be found in the ductal system during an attack of pancreatitis[11–14]. Moreover, ethanol has been shown to result in autoactivation of pancreatic enzymes[15] and Grant *et al.*[16] have suggested a mechanism by which enterokinase, carried in bile, might bring about intraductal activation of zymogens.

If ductal hypertension is important in the pathogenesis of human acute pancreatitis then early ductal decompression may be beneficial in selected cases. Stone *et al.*[17] operated on 36 patients with acute pancreatitis within 73 h of admission to decompress the common bile and pancreatic ducts. They noted inflammation of the ampulla in 89 per cent of cases, with stones in the common bile duct and duodenum in 75 and 31 per cent respectively. They described a sudden 'gush' of pancreatic juice when the ampullary sphincter was divided at sphincterotomy in all patients, suggesting that ductal hypertension was present. This phenomenon was not seen in patients who underwent operation at 3 months. Neoptolemos *et al.*[18] compared early (within 72 h) endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy with conventional treatment for severe acute pancreatitis. The incidence of complications of pancreatitis was 24 per cent with a 4 per cent mortality rate in the ERCP group compared with 61 per cent with an 18 per cent mortality rate in the group treated conservatively.

These studies also demonstrate that the permeable duct cat model of acute pancreatitis has a number of advantages over conventional animal models of the disease. Acute pancreatitis can be produced by physiological manipulations which closely simulate events thought to be important in the pathogenesis of human acute pancreatitis. Furthermore, high pancreatic duct pressures are not required to produce the disease. The peak pancreatic duct pressure generated in the cat pancreatic duct by sodium glycodeoxycholate, ethanol and pancreatic secretion against a > 50 per cent obstruction remained within the physiological range. Aho *et al.*[19] showed that the rat pancreatic duct ruptured at a pressure of 82 mmHg and studies in several species[20] have shown that the maximum pressure generated in the completely obstructed pancreatic duct rarely exceeds 32 mmHg. Despite these observations, several animal models of acute pancreatitis involve the retrograde injection of various substances into the pancreatic duct at pressures up to 140 mmHg. Severe pancreatic damage results from these manoeuvres regardless of the substance injected. It seems unlikely that pressures in this range are ever generated in the human pancreatic duct and the results from experiments using high pressure models should be interpreted with caution.

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Haemorrhage in pancreatic disease

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Haemorrhage is a life-threatening complication in pancreatic disease. Twenty-five patients with this complication are described; 15 had major bleeding, nine had minor bleeding and one patient had a pseudoaneurysm identified at operation. Of the 15 patients with major bleeding, six presented with this complication and in nine cases it followed pancreatic resection. Of the six patients who presented with major bleeding, five underwent resection with one death while the patient managed conservatively died. The nine patients who had major bleeding after pancreatic resection were managed by ligation of the bleeding artery in six cases with one death, and one patient who rebled after ligation of the bleeding artery was successfully managed by further resection. Three patients with postresection major bleeding were managed conservatively with one death. All minor haemorrhages were managed conservatively without mortality. Deaths after major bleeding were a result of sepsis in three cases and respiratory failure in one. The severity of the underlying pancreatitis was an important factor in two patients. Pseudocysts and pancreatic fistulae were important underlying factors leading to the complication. It is recommended that patients with sepsis, a pancreatic fistula or severe underlying pancreatitis should have their haemorrhage treated by pancreatic resection, while those patients with bleeding following pancreatic resection without such complications can be managed by ligation.

Keywords: Haemorrhage, resection, pseudocyst

Haemorrhage is an unusual complication of pancreatic disease, but one which is associated with high morbidity and, indeed, mortality rates when it does occur[1]. Haemorrhage as a complication of pseudocyst formation is well documented[2–4]. A few reports mention haemorrhage in acute pancreatitis without pseudocyst formation[5], and as a result of chronic pancreatitis[1,6,7]. Recently Trede and Schwall have highlighted haemorrhage as a complication of pancreatic surgery with 16 instances in 285 resections[8]. A recent experience with haemorrhage following pancreatic surgery prompted review of this complication in 341 patients who had pancreatic surgery between 1976 and 1987.

Patients and methods

Between 1976 and 1988, 341 operations were performed for benign and malignant pancreatic disease. Twenty-five patients had haemorrhage as a complication of their pancreatic disease. These patients were identified on a retrospective study of the pancreatic surgery database maintained on a prospective basis The haemorrhage was either major and life threatening or minor and almost inconsequential

A major bleed has been defined as one in which the patient presents with a drop in haemoglobin concentration >4 g/dl, has a transfusion requirement of >4 units of packed cells at resuscitation and has evidence of peripheral circulatory impairment. A minor bleed has been defined as one where the patient shows evidence of haemorrhage with minimal or a transient circulatory embarrassment.

Fifteen patients had had a major haemorrhage and nine suffered a minor bleed (*Figure 1*). One patient was noted at operation to have a large pseudoaneurysm as the cause of a mass in the head of the pancreas, and haemorrhage from it was responsible for the sudden clinical deterioration. This patient's bleed is classified as an incidental bleed and he will not be considered further.

Results

Presentation

Major haemorrhage. This group of patients has been subdivided according to whether the patients had a major pancreatic resection or not. In the non-resection group (six patients), all of the patients had acute pancreatitis (four alcohol-related, two gallstone-related), with pseudocyst development in four; one patient had a pancreatic phlegmon associated with massive bleeding following its rupture into the duodenum, and in one patient the pancreatitis occurred following transduodenal sphincterotomy for the extraction of a common bile duct stone complicated by a duodenal perforation and a peripancreatic abscess. In the four patients with pseudocysts, one bled 14 days after cystgastrostomy had been performed, one bled 27 days after an episode of acute pancreatitis, the third patient bled from a pseudoaneurysm 7 months after a pancreaticojejunostomy with choledochojejunostomy Roux-en-Y for alcoholic pancreatitis, and haemorrhage in the fourth

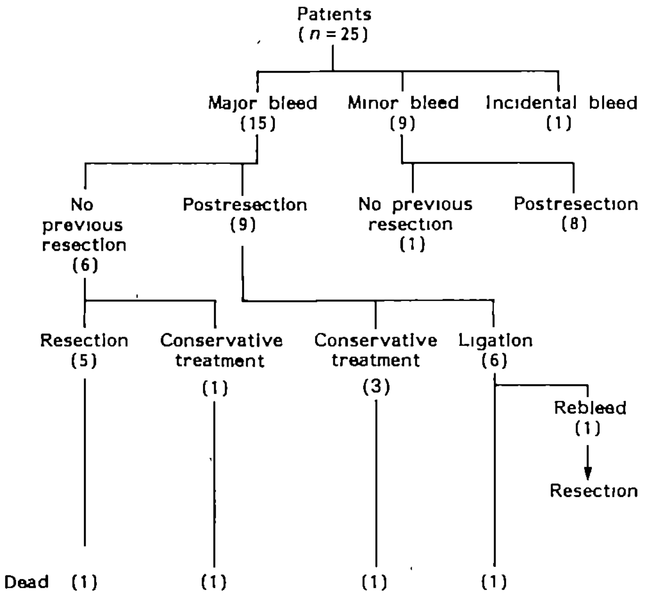

Figure 1 *Analysis of 25 patients with haemorrhage*

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patient occurred after percutaneous drainage (third day after drainage). The first patient was transferred from another hospital with uncontrolled bleeding and the next two were admitted from home on an emergency basis with profuse bleeding. All patients were in pain and two were in respiratory failure.

Nine patients had major postresection haemorrhage. Five of these patients had neoplastic disease and four patients had chronic pancreatitis. The operations previously undertaken in these patients included pancreaticoduodenectomy in two patients, resection of an insulinoma from the head of the pancreas in one patient, a duodenum-preserving resection completing a total pancreatectomy in another, and distal pancreatic resection in five patients. All patients had pain and all had a haematemesis and/or melaena; four of the nine patients had evidence of intra-abdominal sepsis. A pancreatic anastomotic leak identified by either fistula formation or prolonged drainage from a pancreatic drain left *in situ* at operation was present in seven patients. Three of these patients bled through their anastomotic splint drains. A preliminary warning bleed preceded a major haemorrhage by 6 h–10 days in all patients. Major haemorrhages occurred 7–30 days after surgery (median 14 days).

Minor haemorrhage. One patient presented with minor bleeding 2 days after cystgastrostomy, the blood passing along the gastrostomy tube. Eight patients presented after resection, with pain in six, haematemesis or melaena in five, and anastomotic splint haemorrhage in three patients. Three patients had evidence of a pancreatic anastomotic leak. This group includes one patient who had a duodenal leak following a duodenum-preserving resection. Bleeding occurred from 1 to 20 days after the operation.

Investigations

With the co-operation of the endoscopist and radiologist, a multidisciplinary approach was possible in the management of these patients, who were often desperately ill. In the 15 patients with major haemorrhage, upper gastrointestinal endoscopy was undertaken in six patients, ultrasonography in five, computed tomographic (CT) scanning in three and selective arteriography in three patients. In the nine patients with minor haemorrhage, endoscopy was undertaken in two, ultrasonography in three and CT scanning in two patients. It was decided in a number of patients with minor haemorrhage not to investigate further. In some, with major exsanguinating haemorrhage, a decision to operate early was taken after discussion with the radiologist.

Of the three patients in whom arteriography was performed, the site of bleeding was demonstrated in only one patient; embolization was tried, but it failed to control the bleeding. Endoscopy performed in eight patients was contributory in one patient, in whom it revealed a duodenal perforation through which a pancreatic phlegmon had ruptured. Endoscopy diagnosed a bleeding gastric ulcer in one patient who subsequently had a massive haemorrhage from an underlying pseudoaneurysm, and endoscopy was thus misleading

Management

The management of the patients followed accepted practice, with replacement of blood volume as clinically indicated; a decision to operate was made on the grounds of failure to control bleeding by conservative measures. At operation, the easiest technique to control haemorrhage was used, and resection was performed only if it was considered necessary to prevent further bleeding by gaining better control of the bleeding vessel, or by overcoming pancreatic leakage when this was considered to be the underlying cause of bleeding. Jaundice and diabetes added to the difficulties in management.

Major haemorrhage (*Figure 1*). There were six patients who had not previously had resection at the time of haemorrhage; four were managed by initial resection, one by ligature and one conservatively.

In one patient, bleeding from rupture of the splenic artery into a pseudocyst was controlled by distal resection. This patient is well 6 years after resection. The second patient had a pseudocyst treated by a pancreaticojejunostomy and underwent an emergency pancreaticoduodenectomy with good result. The third patient who had a duodenal perforation from acute pancreatitis underwent necrosectomy and salvage pancreatectomy with repair of the duodenal and transverse colonic perforations. He made a rapid recovery and is well 7 years later. The fourth patient, who bled after a transduodenal sphincterotomy, had necrotic pancreatitis with abscess formation; a salvage pancreaticoduodenectomy was undertaken to control a bleeding left gastroepiploic artery but he died 3 h after operation. In the fifth patient, haemorrhage occurred after cystgastrostomy; initially the bleeding vessel was ligated, but rebleeding occurred on day 15. This was controlled by a pancreaticoduodenectomy and the patient is well 7 years later. The sixth patient had a pseudocyst, which was managed conservatively on account of her age (80 years) and respiratory failure; she developed a haemorrhage from which she exsanguinated 35 min later. Transfusion requirements in these six patients ranged from 4 to 28 units.

Of the nine patients who had had previous resection, three were treated conservatively, two of whom did well (one had had a duodenum-preserving completion resection and the other a distal pancreatic resection for an apudoma), although the third patient died in the sixth week after bleeding, from a further haemorrhage. In this last patient an initial episode of bleeding was attributed to a gastric ulcer identified on endoscopy. He was managed medically and surgery was not considered during the subsequent bleed because he had undergone non-curative resection for an aggressive pancreatic carcinoma. This decision was taken despite his age (52 years).

The bleeding artery was ligated in the six patients in whom haemorrhage was surgically controlled. The site of bleeding was the splenic artery (two patients), the gastroduodenal artery (one patient), the inferior pancreaticoduodenal artery (one patient) and the hepatic artery (two patients). Both patients who bled from the hepatic artery had further haemorrhage. This was fatal in one patient, who was 70 years old, jaundiced and who had an aggressive carcinoma. The other patient also with neoplastic disease had a further ligation with distal resection as he was found at operation to have a small retropancreatic abscess. This patient survived. Two patients with a splenic artery bleed required reconstruction of their pancreaticojejunal anastomosis as these had been opened to gain access to the site of haemorrhage. The transfusion requirement was 4–42 units.

Minor haemorrhage. The single patient with minor haemorrhage who had not had a resection experienced bleeding after cystgastrostomy and was treated conservatively and successfully for presumed suture line haemorrhage. Eight patients had a minor bleed following resection, and all were managed conservatively and successfully. Their site of bleeding remains unknown. All minor haemorrhages were regarded as potential warning bleeds and the patient was watched with care as an in-patient for at least 7 days.

The last patient in our series underwent a difficult pancreaticoduodenectomy for a pseudoaneurysm which was identified at operation, having presented preoperatively as a mass in the head of the pancreas. Haemorrhage from this was contained within the leaves of the transverse mesocolon and was responsible for sudden clinical deterioration in this patient; he was cured by a pancreaticoduodenectomy.

Discussion

This paper describes haemorrhage in relation to pancreatic disease. Massive haemorrhage in severe pancreatitis is well documented. Stroud *et al.*[5] described 15 cases with a mortality

Table 1 *Summary of previous descriptions of haemorrhage associated with pancreatic disease*

				Haemorrhages (*n*)					
Operation	Reference	*n*	Mortality (%)	Total	Gastro-intestinal	Intra-abdominal	Mortality (%)	Pancreatic leak (%)	Sepsis (%)
Pancreaticoduodenectomy	13	88	19	16	12	4	56	14	23
Total pancreatectomy	14	83	4·8	4	2	2	50	—	7/83
Pancreaticoduodenectomy	15	279	12·5	31	NR	NR	58	20	57
Pancreaticoduodenectomy	16	103	10·6	6	5	1	—	14·5	—
Various	17	177	6	10	5	5	—	6	7
Pancreaticoduodenectomy	8	285	3·1	16	12	4	6·25	8·8	2·4

NR, not recorded

rate of 53 per cent, the patients with pseudocysts showing the highest survival rates. Their transfusion requirements of 8–177 units highlight the magnitude of the problem.

Chronic pancreatitis as a cause of gastrointestinal bleeding is well described[6,7]. Bleeding through the pancreatic duct is a particularly difficult diagnostic problem[9–11] Investigations can be inconclusive[12] but, despite false negative results, coeliac axis angiography is recommended[7] although the authors do accept that it is often non-contributory. It is documented that 10 per cent of patients with chronic pancreatitis have associated pseudoaneurysms[1].

Description of postresection haemorrhage is inadequate. The reported incidence varies from 5 to 19 per cent[13,14] and in our experience it was 9·5 per cent in patients with pancreatitis and 7·5 per cent in patients with neoplasms. The mortality rates range from 6 to 58 per cent (*Table 1*). In most series, haemorrhage is mentioned only in passing but, on close study, the incidence and risk of mortality from postresection bleeding in many reports reflect closely the mortality rate of the series.

Jordan[18] reported seven deaths in 16 patients with pancreatic fistulae that complicated 63 pancreaticoduodenectomies. In four of the seven cases it was due to postresection haemorrhage, the gastroduodenal artery being the usual source. Trede and Schwall[8] highlight the occurrence of postresection complications around the pancreatic anastomosis. Haemorrhage in this series of 285 pancreaticoduodenectomies was the second most frequent complication occurring in 16 (5·6 per cent) cases with one death, which they attribute to delayed operation. In the series reported by Trede and Schwall the increased mortality rate following haemorrhage and pancreatic leaks in the jaundiced patient is well demonstrated. All of their patients had endoscopy at the onset of bleeding. The severity of bleeding in their patients is not documented. Four patients were managed with endoscopic laser or injection treatment. Of the remaining 12 patients, eight patients with gastrointestinal bleeding and four patients with retroperitoneal haemorrhage required ligation of the bleeding vessel. The management of patients at risk of recurrent haemorrhage is difficult and many techniques have been tried, such as continuous irrigation of the operation site via catheters placed at the time of operation[15]; of the techniques described, completion resection appears to be the logical choice[19]. The presence of sepsis, jaundice and glandular friability are important factors which are responsible for the increased risk of mortality following pancreaticoduodenal resection[15].

Our experience favours early resection in non-resected patients who develop major bleeding as four of the five patients so treated achieved good results. Haemorrhage in patients with pseudocysts is described as spontaneous or postoperative (i.e. following drainage). Internal drainage does not afford any protection from bleeding, although there are suggestions that pseudocystjejunostomy Roux-en-Y may be associated with a lower incidence of stomal suture line bleeding. Even if this were true, the operation will not prevent haemorrhage from an underlying pseudoaneurysm. This is also apparent from series reporting as many preoperative as postoperative cases of haemorrhage[2,3]. Frey *et al.*[20] recommended primary excision of the cyst, and suggest that ligation of the bleeding vessel in the presence of pancreatitis is unlikely to succeed. Acute pancreatitis with haemorrhage managed conservatively may be associated with a 100 per cent mortality rate[21]. Surgery, which has by some been considered ill advised, will with adequate intensive care support improved survival figures[20–23]. We have not been able to evaluate the role of embolization, which has been well documented in a complementary capacity[24]. The literature is now replete with reports of successful embolization of major arterial bleeding and of several pseudoaneurysms[25–28]. This is probably the way forward in reducing the risk of mortality from haemorrhage in these gravely ill patients, but the skill required for embolization is considerable.

The occurrence of warning haemorrhages in postresection patients has not been described previously. These are similar to minor haemorrhages but preceded major bleeding by 6 h–10 days. They occurred in all postresection major bleeds, and serve to emphasize the importance of watching carefully all episodes of bleeding, however small, in the postresection patient. In our experience, postresection bleeds in chronic pancreatitis (four patients) were safely managed with ligation. Of the five patients in the neoplastic group who had major bleeding, two deaths were due to 'inadequate' surgical management. Early ligation is the treatment of choice in the absence of sepsis or fistula formation, and resection should be considered if either is present. Investigations in the presence of major haemorrhage are often unhelpful and should be undertaken only after close consultation with the appropriate specialist, who must have experience in these techniques The difficulty with endoscopy and imaging is mainly related to the fact that haemorrhage occurs near the pancreaticojejunal anastomosis and passes down the jejunal loop. Thus endoscopy is often negative while ultrasonography or CT scanning show no abnormality unless associated with an abscess or a pseudocyst. Angiography may well be the only investigation that will elucidate the source of bleeding. Unfortunately, the bleeding is often massive and intermittent, and thus missed at angiography. The use of angiography in our hands proved disappointing, and it was used sparingly. Early resuscitation and operation will be indicated in many patients, especially in those with underlying sepsis or fistula formation. Angiography at the warning-bleed stage may identify patients with vascular lesions amenable to embolization.

We recommend that major non-resection haemorrhage should be managed by early resection, while major postresection bleeding in patients with underlying chronic pancreatitis can be treated with ligation and, if need be, with reconstruction of a failed pancreatic anastomosis. However, in the presence of sepsis, abscess formation or an established pancreatic fistula, resection of the remaining pancreas should be considered

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Endoscopic management of inoperable cholangiocarcinoma using iridium-192

We report a well tolerated endoscopic technique of administering intraluminal radiotherapy to 14 patients with inoperable cholangiocarcinoma, in which the iridium-192 wire source was inserted down a nasobiliary catheter placed within a previously inserted endoscopic biliary prosthesis, thus allowing bile flow to continue during treatment. Radiotherapy was commenced 2 weeks after biliary decompression, when the median serum bilirubin level had fallen from 213 to 34 μmol/l. A total radiation dose of 6000 cGy at 0·5 cm from the source was administered over a median of 85 h (range 77–116 h). In four patients there was a transient increase in serum bilirubin during iridium treatment and, in two cases (14 per cent), this was associated with mild cholangitis. Both cases resolved rapidly once the iridium wire and nasobiliary catheter were removed. The median hospital stay after treatment was 2·5 days (range 0–28 days). The late complications associated with stent blockage were minimized by routinely changing stents at 4–6-monthly intervals; ten of the patients have so far undergone from one to five (median three) stent changes. Five patients have died at 3·6–8·2 months (median 4·8 months) following iridium treatment; four had extensive type III hilar lesions at diagnosis. Nine patients are still alive at 5·4–31·0 months (median 16·4 months). The overall median survival after iridium therapy is 10·5 months. This technique of endoscopic biliary decompression before internal iridium administration minimizes complications by allowing biliary drainage during treatment. The role of this treatment in patients with inoperable cholangiocarcinoma awaits the results of randomized, controlled trials.

Keywords: Cholangiocarcinoma, iridium-192

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Cholangiocarcinoma is a relatively slow-growing tumour which rarely metastasizes[1]. Complete surgical resection is possible in only 10–20 per cent of cases[2–4] and preliminary results of hepatic transplantation are disappointing, with death usually occurring in the first year. Thus the majority of patients are managed palliatively with relief of biliary obstruction either surgically or by endoprosthesis insertion. Unfortunately, the survival of patients undergoing palliative surgical bypass (8–10 months)[3–5] or transhepatic prosthesis insertion (3–9 months)[4–6] is limited, predominantly because of local extension of the tumour resulting in further biliary obstruction, recurrent episodes of cholangitis, liver failure, sepsis, haemorrhage and death.

Although these tumours were originally considered to be resistant to radiotherapy, more recent studies have suggested that this is not the case[6–9]. Since 1981, a number of groups have reported the use of internal radiotherapy using iridium-192 inserted surgically or transhepatically in patients with bile duct carcinoma[10–17]. The morbidity and mortality rates associated with percutaneous endoprosthesis insertion appear to be higher than that experienced with the endoscopic route[18]. In a recent study of 24 patients with malignant biliary obstruction, treatment with iridium-192 inserted via an endoscopically placed nasobiliary tube with subsequent endoprosthesis insertion was associated with a 30 per cent incidence of early cholangitis[17]. This high incidence is possibly due to poor biliary drainage during the period of intraluminal irradiation. The present study reports the endoscopic administration of internal iridium-192 radiotherapy in 14 patients with inoperable cholangiocarcinoma who had undergone prior biliary decompression by endoscopic endoprosthesis insertion.

Patients and methods

Patients

Fourteen patients (ten men, four women) aged 41–80 years (median 60 years) with cholangiocarcinoma involving the bifurcation of the bile duct, seen between February 1986 and June 1988, were deemed inoperable on the basis of laparotomy (four patients) or various imaging techniques (ultrasound, computed tomography (CT) scan, arteriography: eight patients), or due to age and poor general medical condition (two patients). The initial diagnosis was based on the characteristic appearances of cholangiocarcinoma on endoscopic retrograde cholangiopancreatography (ERCP) with an abnormal cholangiogram but a normal pancreatogram, a normal upper gastrointestinal endoscopy, and no obvious clinical evidence of a distant primary neoplasm. Nine patients had type III hilar lesions based on the Bismuth classification[19]. In five of these patients there was extensive involvement of the intrahepatic ducts (recently classified as type IV)[4]. The remaining five patients had type II lesions. The diagnosis was confirmed histologically in ten patients: in four patients at prior laparotomy, in two patients by cytological examination of tumour brushings, in one patient by percutaneous biopsy and in three patients at post-mortem examination.

Jaundice had been present for between 2 and 10 weeks (median 5 weeks) at the time of diagnosis, when the median serum bilirubin was 213 μmol/l (range 27–415 μmol/l).

Methods

At initial ERCP a 10 Fr prosthesis (Cotton–Leung biliary stent, Wilson–Cook Medical Incorporated, Winston-Salem, North Carolina,

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USA) was inserted through the tumour with its distal end protruding 1–2 cm into the lumen of the duodenum. All patients received antibiotics (amoxycillin and gentamicin) intravenously before and for 48 h after endoprosthesis insertion and, provided the bilirubin level was falling satisfactorily, were discharged home after 48–72 h. Patients were readmitted approximately 2 weeks later once the serum bilirubin had fallen and their general medical condition improved. A second examination using ERCP was performed and the biliary prosthesis was cannulated with a 6 Fr Teflon® (E.I. du Pont de Nemours and Company, UK) guiding catheter (Meadox-Surgimed, Stenløse, Denmark), which was positioned at the top of the prosthesis and the upper and lower limits of the stricture were defined radiologically. The endoscope was then removed and the Teflon catheter was rerouted through the nose and allowed to drain freely. A length of iridium-192 wire long enough to overlap the upper and lower margins of the stricture by a minimum of 1 cm was loaded into the tip of a standard radiological Teflon-coated movable-core guidewire (35×10^{-3} inch diameter; Tefcore®, William Cook Europe, Bjaeverskov, Denmark; *Figure 1*). This was inserted into the nasobiliary catheter and the iridium source was positioned at the level of the stricture under radiological control (*Figure 2*). The nasobiliary catheter was then connected to a sealed bag system to allow for bile drainage around the guidewire. Patients were nursed in a side room and surrounded by lead screens. Intravenous antibiotics were administered for the duration of the iridium-192 therapy which ranged from 77 to 116 h (median 85 h), depending on the length and activity of the iridium wire used. All patients received a total dose of 6000 cGy at 0·5 cm from the source. Once the radiotherapy was completed, the iridium wire and Teflon catheter were removed under fluoroscopic control, leaving the endoscopic stent *in situ*.

Results

Endoscopic insertion of the prosthesis was completely successful on the first occasion in 11 of the 14 patients. In the remaining three patients, the stricture was too tight to dilate fully; a nasobiliary catheter was inserted in one patient and in the other two patients a percutaneous transhepatic catheter was left *in situ*. In all three patients it was subsequently possible to insert an endoscopic prosthesis. All patients received intraluminal radiotherapy with iridium-192 and most patients were discharged home within a few days of completing this treatment; the hospital stay after the procedure ranged from 0 to 28 days (median 2·5 days). The median serum bilirubin level was 213 μmol/l (range 27–415 μmol/l) before biliary decompression and fell to 34 μmol/l 2 weeks after stent insertion and to 24 μmol/l by the time of discharge following iridium treatment.

There were no deaths within 30 days and few early complications following iridium therapy. In four patients there was a transient increase in serum bilirubin during iridium treatment, and in two cases (14 per cent) this was associated with mild cholangitis despite prophylactic antibiotics. Both cases resolved rapidly once the iridium wire and nasobiliary catheter were removed. One patient experienced mild nausea while the iridium source was *in situ*. One patient, in whom the iridium wire and nasobiliary tube were removed without fluoroscopic control, was readmitted 4 days later with increasing jaundice and cholangitis due to dislodgement of the prosthesis.

In order to avoid late complications associated with stent blockage (particularly recurrent jaundice and cholangitis), endoprostheses were changed routinely at intervals of 4–6 months. Ten of the patients have so far undergone from one to five (median three) stent changes and there have been only two episodes of cholangitis and three episodes of jaundice due to blocked endoprotheses. In one patient with a type III lesion, it was necessary to insert stents into both hepatic lobes to provide adequate biliary drainage and relieve cholangitis.

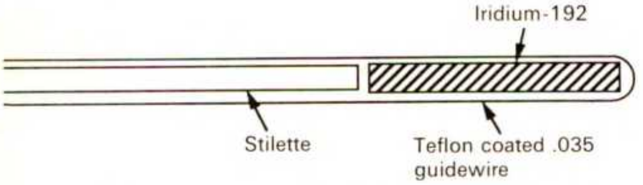

Figure 1 *Schematic representation of an iridium-192 wire within a movable-core guidewire. The guidewire stilette is reinserted until the length of iridium wire is located at the distal end of the guidewire*

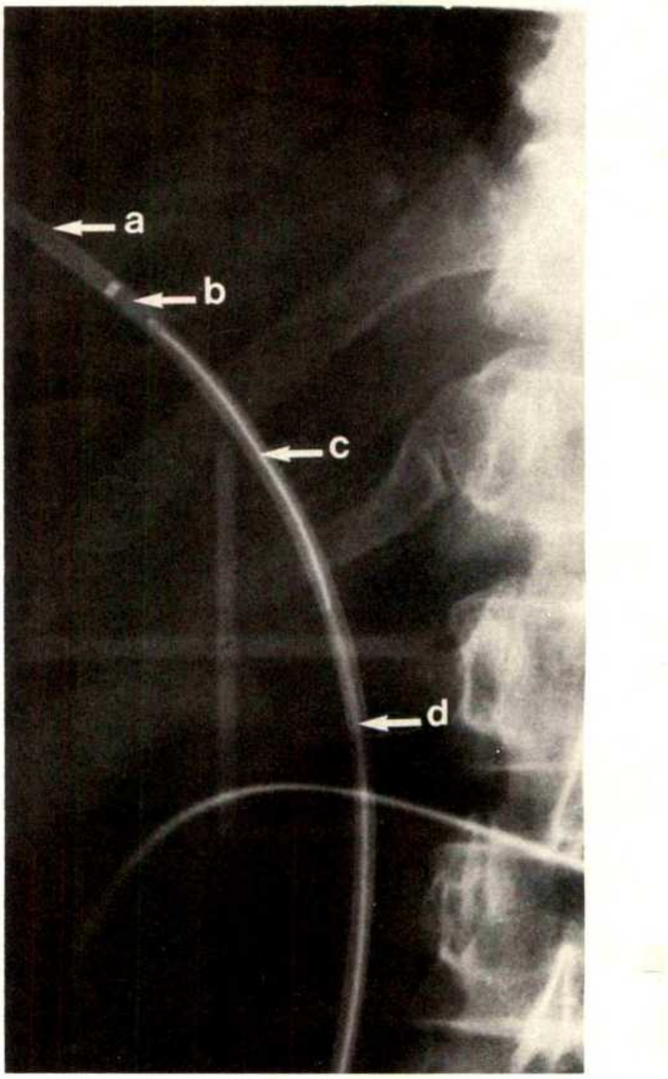

Figure 2 *Radiograph of an iridium-containing guidewire inserted into a nasobiliary catheter which has been inserted into an endoscopic stent. A radio-opaque marker at the distal tip of the nasobiliary catheter allows precise placement of the iridium wire across the malignant stricture. Labelled arrows indicate the endoscopic stent* (*a*), *the nasobiliary catheter with distal radio-opaque marker* (*b*) *and the iridium-192 wire* (*c*) *within the movable-core guidewire* (*d*)

Five patients have died at 110–249 days (median 146 days) after iridium treatment. Four of these patients had type III cholangiocarcinomas with extensive involvement of the intrahepatic bile ducts at diagnosis. Nine patients are still alive at 165–942 days (median 498 days). The overall median survival after iridium therapy is 318 days (10·5 months).

Discussion

A number of studies have suggested that the survival of patients with biliary obstruction due to cholangiocarcinoma may be improved by using internal radiotherapy in addition to palliative biliary decompression[14-16]. However, substantial morbidity and mortality rates have been reported with this technique, particularly related to the percutaneous transhepatic approach[14] and also to the high incidence of early cholangitis, ranging from 30 to 40 per cent[10,14,17]. In the present study, the 30-day mortality rate was zero and the incidence of cholangitis associated with insertion of the iridium-192 wire was 14 per cent. This figure is similar to that reported with the insertion of an endoscopic endoprosthesis alone[18]. The substantially lower incidence of cholangitis in the present study is possibly related to the policy of relieving the biliary obstruction by endoprosthesis insertion before placement of the iridium-192 wire. In this way biliary drainage is maintained around the nasobiliary tube and iridium-192 wire during the course of treatment. It is also possible that the improvement in the general condition of patients observed when jaundice is alleviated may be associated with a lower incidence of complications. The problem of impaired bile flow during iridium-192 treatment may, in the future, be solved by the use of high-dose-rate, remote afterloading devices which can deliver the same dose of iridium-192 in a single treatment over minutes[20].

The median survival time in this series compares favourably with that of patients undergoing palliative surgery and is similar to that reported following radical resection[3–5]. However, a definite role for internal iridium-192 in the treatment of cholangiocarcinoma has not been confirmed in a randomized controlled trial. Iridium-192 emits predominantly γ radiation, which causes an intense but localized radiation field resulting in minimal radiation damage to the surrounding organs. Radiation doses in excess of 4000 cGy have been reported to improve survival in patients receiving external radiotherapy[7,9], but the optimal radiation dose and treatment regimen for cholangiocarcinoma has yet to be determined. Indeed, it is possible that a combination of internal and external radiotherapy, which provides a more uniform radiation field[11,21], might offer the best chance of long-term survival. Clearly, all future trials should stratify patients according to the site and extent of the tumour as survival is progressively worse in patients with extensive intrahepatic spread[4]. This point is highlighted in the present study where four of five patients with extensive type III (type IV) hilar strictures died of their disease 4–8 months after treatment, whereas nine patients with type II and less extensive type III lesions are still alive at a median of 16·4 months. This compares favourably with the Middlesex Hospital experience of stenting alone for cholangiocarcinoma, where the median survival time for type II and type III lesions was 4 and 3 months respectively[22].

The results of the present study are encouraging. The technique was well tolerated and associated with an acceptably low complication rate. In addition, a policy of routinely changing stents every 4–6 months has minimized the long-term complications of stent blockage, particularly recurrent jaundice and cholangitis[16]. A randomized, controlled trial comparing endoscopic stent insertion with or without radiotherapy has recently been set up to assess our initial impression that survival in patients with inoperable cholangiocarcinoma is improved by intraluminal iridium-192.

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Reconstruction of chest wall defects with homologous dura mater grafts

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Resections of chest wall tumours leave the surgeon with the challenging problem of reconstructing the defect. The objectives of reconstruction of full-thickness defects of the chest wall are threefold: firstly, to provide chest wall stability in order to prevent paradoxical respiration movements or herniation of the lung; secondly, to cover and protect vital organs; thirdly, to achieve the above in a cosmetically satisfactory way. Procedures using autologous materials such as periosteal or muscular flaps, or fascia lata are tedious, time consuming, often unsightly and may provide little rigidity. Because of their simple applicability and mechanical properties, synthetic materials such as Teflon® (du Pont de Nemour Inc., UK) and Marlex® mesh (C.R. Bard Inc., Massachusetts, USA) have been used with increasing frequency in recent years. However, these non-absorbable materials have disadvantages in the face of chronic infection.

To avoid these specific disadvantages dura mater grafts have been successfully used for tympanoplasties, replacement of the tracheal wall, closure of fistulae and reconstruction of the urinary bladder[1–3]. Successful application of dura mater in the reconstruction of abdominal wall defects[4] lead to its use in chest wall defects When the size of the chest wall defect necessitated replacement of soft tissue this was done by transposition of the greater omentum, covered with split skin grafts[5].

Here we report on our experience in reconstructing chest wall defects with homologous dura mater grafts in 14 patients

Patients and methods

Methods

In 1985 and 1986 partial resections of the chest wall were performed in 14 patients. In all but two patients the resection included part of the sternum. Chest wall defects ranged from 5 × 4 cm to 12 × 18 cm (average 10 × 10 cm) Homologous dura mater grafts (Lyodura®, B. Braun A.G., Melsungen, FRG) were used The human dura mater grafts have been lyophilized, freeze-dried and are immunologically inert[6] As its maximum size is 6 × 14 cm, several grafts may have to be patched together in order to close a large chest wall defect With some tension the graft is fixed to the periosteum, perichondrium and/or fascia by a running suture with polydioxanone In five patients the dura mater graft had to be covered by a pedicled greater omentum transposition which in turn was covered with meshed split skin grafts No suction was applied to the wound or the thorax.

Patients

Of the 14 patients treated, three had primary sarcomas. The remainder had secondary tumours (nine patients with a local recurrence or retrosternal metastases of breast cancer, one patient with a retrosternal recurrence of a thymoma, and one patient with a retrosternal isolated metastasis of ovarian cancer). Two of the patients with breast cancer had ulcers associated with osteomyelitis and extensive radiologically induced necrosis which prompted resection. Median follow-up was 18 months (range 10–24 months).

Results

Chest wall repair was successful in all but one patient. In this patient a partial disruption of the graft on the medial side occurred during very high positive end expiratory pressure mechanical ventilation given during a long period of adult respiratory distress syndrome. This complication led to permanent paradoxical respiratory movements at this site. In all other patients the results were very favourable. Restoration of the stability of the chest wall by the dura mater grafts was excellent, especially when an omentoplasty was performed. Within 2–3 months the implant underwent a rigid transformation.

No paradox was observed in any of the patients; mechanical properties were very good. Two complications unrelated to the use of dura mater homografts occurred· a haemothorax in one patient and rupture of the diaphragm that was subsequently repaired with a dura mater implant in another.

Discussion

The results of reconstruction of chest wall defects with homologous dura mater grafts in the 14 patients described above have been satisfactory. Restoration of the stability of the chest wall has been excellent. The rigidity that is obtained when dura mater grafts are used in combination with transposition of the greater omentum in order to close large defects is remarkable. Moreover the absence of infectious complications is significant and underlines the ideal biological properties of these biografts. The simplicity of the surgical procedure, the chest wall stability and the resistance to infectious complications suggest that these homografts may well be superior to the synthetic materials commonly used. Complications related to the material were not observed. The risk of acquiring Jakob–Creutzfeldt disease after implantation of a dura mater allograft, which has been claimed in one case report[7], has not been substantiated in this or any other series.

After a follow-up period of 10–24 months (median 18 months), during which two patients died from widespread metastatic disease, only one local recurrence occurred.

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Adverse effects of preoperative hepatic artery chemoembolization for resectable hepatocellular carcinoma: A retrospective comparison of 138 liver resections

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*During the past 8 years we have treated 268 patients with primary hepatocellular carcinoma (HCC); total extirpation of the tumor was carried out in 138. Thirty-one of the patients with resectable HCCs had already been treated with transcatheter arterial embolization (TAE) of the liver before they were referred to us. The clinical values of preoperative TAE were retrospectively evaluated for those 31 patients and for the remaining 107 patients without TAE. There were no substantial differences between the two study groups in the clinical and histopathologic backgrounds. No differences were observed in the extent of liver resection, estimated blood loss during surgery, and operation time. During surgery, however, troublesome intra-abdominal complications relevant to TAE were encountered in 15 patients, and detection of tumors was impossible, even with intraoperative ultrasonography, in five patients in the group with TAE. Such findings were not present in any of the patients without TAE. Postoperative morbidity and mortality rates were similar in the two groups. There was no significant difference in the rate of recurrence of tumor in the liver, but the recurrence time was significantly shorter in the group with TAE. TAE did not improve the long-term survival rates in patients either with or without cirrhosis. Results of our study seem to indicate that preoperative TAE is meaningless in the treatment of resectable HCCs and therefore should be avoided, particularly in patients with advanced cirrhosis of the liver. (*S*URGERY 1989;106:81-6.)*

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HEPATOCELLULAR CARCINOMA (HCC) is one of the most malignant tumors in human beings, and its incidence has been increasing all over the world. The prognosis for those with HCC is usually dismal without treatment.[1,2] Because of its biological characteristics, with early intrahepatic spread and invasion of the portal or hepatic veins or a high incidence of associated cirrhosis of the liver, the resectability rate of this tumor is low.[3-5] However, hepatic resection is at present the most reliable and acknowledged method for permanent cure of patients with HCC, although liver transplantation may be preferable in selected patients.[6] Since its initial use for treatment of nonresectable malignant tumors of the liver,[7] embolization of the hepatic artery has been widely used with a great deal of evidence that this technique in combination with cytostatic drugs is a useful palliative alternative.[8-15]

During recent years in Japan, transcatheter arterial embolization (TAE) of the liver has been performed extensively not only for palliative purposes[13,14] but also as a preoperative adjuvant, even in patients with resectable HCCs, with the hope that TAE before hepatic resection may improve the survival rate.[16-19] From a surgical viewpoint, TAE before liver resection may have several disadvantages and possible benefits.

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Table I. Clinical background in patients with and without preoperative embolization of the hepatic artery (TAE)

Data	*With TAE (n = 31)*	*Without TAE (n = 107)*
Age (yr)	56.5 ± 9.1	59.4 ± 8.9
Male/female	25/6	90/17
Duration of liver disease (yr)	6.5 ± 7.3	8.5 ± 8.3
Alcohol abuse*		
Yes	14	49
No	17	58
Liver cirrhosis		
Yes	26	88
No	5	19
Child's grade[20]		
A	17	69
B	13	32
C	1	6
Hepatitis B virus		
HBs-Ag positive	12†	19†
Anti-HBs positive	7	25
Anti-HBc positive	22	59
None	8	21
Serum alpha-fetoprotein (ng/ml)		
0-20	13	27
21-100	5	24
101-1000	10	31
More than 1000	3	21
Time between diagnosis and operation (days)	152 ± 228‡	46 ± 45‡

*Those who consumed more than 50 gm of alcohol a day for more than 5 years

†$p < 0.02$

‡$p < 0.01$

The purpose of this study was to retrospectively compare the results of hepatic resection in 31 patients with and 107 patients without preceding TAE therapy and to evaluate the genuine role of preoperative TAE in resectable HCC.

MATERIAL AND METHODS

From January 1980 to March 1986, 228 patients with primary HCC were admitted to the Department of Surgery, Hiroshima Red Cross and Atomic Bomb Hospital. From April 1986 until December 1987, another 40 patients with HCC were treated in this department. Thus a total 268 patients with HCC were serially treated during an 8-year period. Total extirpation of the tumor was carried out in 138 patients (51.5%). No preceding therapy had been given to 107 patients before liver resection, whereas the remaining 31 patients had undergone TAE at other hospitals. Results of imaging studies and liver function tests before TAE in these 31 patients were retrospectively evaluated by us, and it was confirmed that all of the tumors would have been resectable from the beginning. All of these patients were followed up by their physicians for 7 to 1245 days (130 ± 234 days) after TAE but were referred to us for liver resection because of either reelevation of the serum alpha-fetoprotein level, reenlargement of the tumor, or patient's desire.

Table II. Postoperative complications

Complication	*With TAE (n = 31)*	*Without TAE (n = 107)*
Liver failure	3	14
Right pleural effusion	1	7
Postoperative bleeding	1	6
Upper gastrointestinal bleeding	1	3
Biliary fistula	1	2
Pancreatitis	1	1
Pneumonia	1	1
Adult respiratory distress syndrome	1	
Other	3	8

Method of TAE. TAE had been performed by the Seldinger technique in all instances. The mean interval between the diagnosis of HCC and the time of TAE was 22 days. Patients were then followed up for a mean of 130 days until liver resection. The embolization materials used were gelatin sponge cubes or powder in 12, oil contrast lipiodol in 14, and both materials in five patients. Thirty patients concomitantly had infusion chemotherapy with doxorubicin (Adriamycin) (10 to 60 mg) in 20, mitomycin C (6 to 20 mg) in eight, and a combination of the drugs in two instances.

Preoperative clinical background. There were no significant differences in clinical background between those with and without preoperative TAE. Only the time interval between diagnosis and operation was different (Table I). There were no differences in results of preoperative liver function tests including serum transaminase activities, serum bilirubin and albumin concentrations, and Bromsulphalein (BSP) test.

Preoperative associated conditions. Diabetes mellitus, esophageal varices, cholelithiasis, and gastroduodenal ulcer were the most common complications in the groups both with and without TAE; 9 and 29, 10 and

13, 1 and 9, and 2 and 5, respectively. The incidence of the varices was significantly higher in the group with TAE ($p < 0.01$), but no substantial difference was noted for other complications.

Statistical methods. Statistical comparisons for significance were carried out with unpaired Student *t* and χ^2 tests. A *p* value of less than 0.05 was considered statistically significant. All of the data in the tables are shown as actual number of patients or mean ± standard deviation. Cumulative survival rates were obtained by means of the Kaplan-Meier method.

RESULTS

Type of liver resection. Major hepatic resection was considered a resection equal to or larger than left lobectomy. Therefore left lateral segmentectomy, that is, the double segmentectomy of Couinaud,[21] was included in the group undergoing minor resection. Major resection was performed in 18 patients without TAE and three patients with TAE. There was no difference in the extent of liver resection between the groups with and without TAE.

Blood loss and operation time. The estimated blood loss during surgery ranged from 40 to 12,000 ml (1541 ± 1754) in the group without TAE and from 100 to 7100 ml (1497 ± 1977) in the group with TAE; there was no statistical difference. The operation times were also similar: 125 ± 57 minutes in the group without TAE and 123 ± 51 minutes in the group with TAE.

Intraoperative findings. Fifteen patients with TAE had such troublesome complications as severe adhesions, infarction of the gallbladder with or without perforation, liver infarction, or intrahepatic abscess formation. Intraoperative ultrasonograms showed the presence of tumor in all patients without TAE but not in five patients with preceding TAE.

Postoperative complications. There were 42 postoperative complications in 31 patients without TAE, whereas in eight patients with TAE there were only 13 complications. There were no differences in the incidence and type of complications (Table II).

Postoperative mortality. Nine patients died within 1 month and another eight died 1 to 3 months postoperatively. The cause of death was liver failure in all 17 patients. The overall hospital death rate was 13% in the group without TAE and 10% in the group with TAE. The mortality rate in the 107 patients without TAE increased according to the Child's grade (Table III).

Postoperative chemotherapy. Postoperative chemotherapy was given to 69 patients. There were no differences in the rate and method of chemotherapy between the two study groups (Table III).

Table III. Postoperative data

Data	*With TAE (n = 31)*	*Without TAE (n = 107)*
Postoperative complications		
Yes	8	31
No	23	76
Postoperative death		
Within 1 mo	1 (3.2)	8 (7.5)
After 1 mo	2 (6.5)	6 (5.6)
Overall	3 (10.0)	14 (13.1)
Child's grade		
A	0	5 (7.0)
B	3 (23 0)	7 (21 9)
C	0	2 (33.3)
Postoperative chemotherapy*		
Yes	20	49
No	8	44
Follow-up time (mo)	26 ± 20†	48 ± 19†
Recurrence*		
Yes	13	48
No	15	45
Time of recurrence (mo)		
From diagnosis	11 2 ± 4.7‡	17 6 ± 9 8‡
From operation	7.4 ± 4.3§	16 0 ± 9 8§

Figures in parentheses indicate percentages
*Operative deaths are excluded
†$p < 0\ 01$
‡$p < 0\ 05$
§$p < 0\ 01$

Recurrence of tumor. Although the follow-up time was significantly different, the rate of recurrence of tumor in the residual liver was similar in the two groups. The mean time of recurrence from either the time of the diagnosis of HCC or liver resection was significantly shorter in the group with TAE compared to the group without TAE (Table III).

Histopathologic comparison. There were no differences between the two groups in the type and size of HCC, incidence of daughter nodules, grade of tumor differentiation, or underlying liver disease. Tumor necrosis was found in all patients with TAE, but only in three was the necrosis so severe that histologic diagnosis of the type and Edmondson's grade of HCC was impossible (Table IV).

Cause of late death. During the follow-up period 50 patients in the group without TAE died; causes of death included recurrence of tumor in 39, liver failure in four, gastrointestinal bleeding in four, hepatitis in two, and gastric cancer in one. Eight patients in the

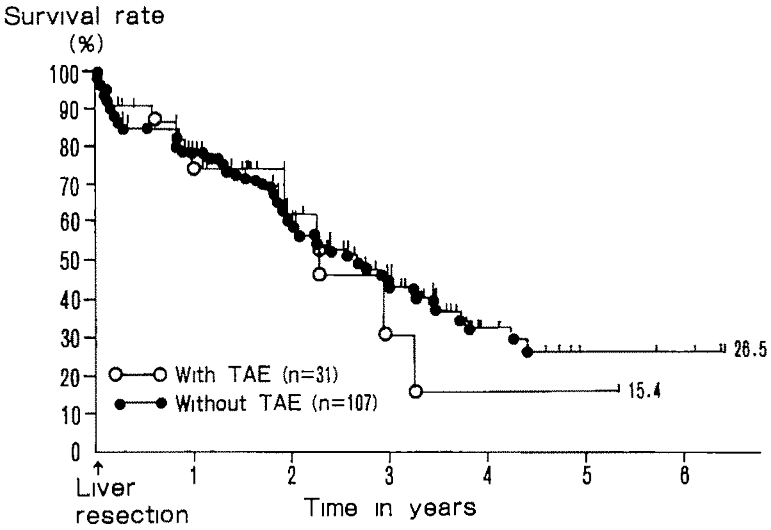

Fig. 1. Cumulative survival rates after liver resection in 31 patients with and 107 patients without preoperative TAE of the liver. There was no significant difference between the two groups.

Table IV. Histopathologic data

Data	*With TAE (n = 31)*	*Without TAE (n = 107)*
Tumor type		
Nodular	23	82
Massive	7	25
Tumor size		
<3 cm	14	35
>3 cm	17	72
Daughter nodule		
Yes	9	40
No	22	67
Histologic type of HCC		
Trabecular	20	89
Compact	2	3
Pseudoglandular	2	1
Clear cell	0	1
Mixed	4	13
Necrosis	3*	0*
Edmondson's grade[22]		
I	0	2
II	13	53
III	3	9
Mixed	13	43
Unknown	3†	0†
Underlying liver disease		
Liver cirrhosis	26	88
Chronic hepatitis	5	18
None	0	1

*$p < 0.001$

†$p < 0.001$

group with TAE died, seven of recurrence and one of sepsis. No statistical difference was seen.

Long-term survival. The cumulative survival rates after liver resection including operative deaths in the group without TAE and the group with TAE were 77% and 75% at 1 year, 57% and 62% at 2 years, 45% and 31% at 3 years, 33% and 15% at 4 years, and 27% and 15% at 5 years, respectively. There was no difference between the two groups (Fig. 1). Even when the survival rates after the diagnosis of HCC were compared, no significant difference was observed between the two study groups (Fig. 2). Thus, preoperative TAE did not influence long-term survival.

DISCUSSION

Despite marked advances in diagnostic methods and surgical techniques, the resectability rate of HCC is usually low.[3-5] This may be attributable to a high incidence of associated cirrhosis of the liver and the rapid growth of this tumor.[1,2] In Japan, where ultrasonography is used extensively, the incidence of relatively small HCCs has increased in recent years. In fact 49 of 138 patients in our current series had HCCs smaller than 3 cm. We have already shown that such small HCCs are frequently resectable, even in the presence of cirrhosis, by minor hepatic resection.[23,24] In this study the resectability rate was 51.5%. Probably this high rate can be explained mostly by this high incidence of small HCCs.

Even after total extirpation of HCC, the recurrence

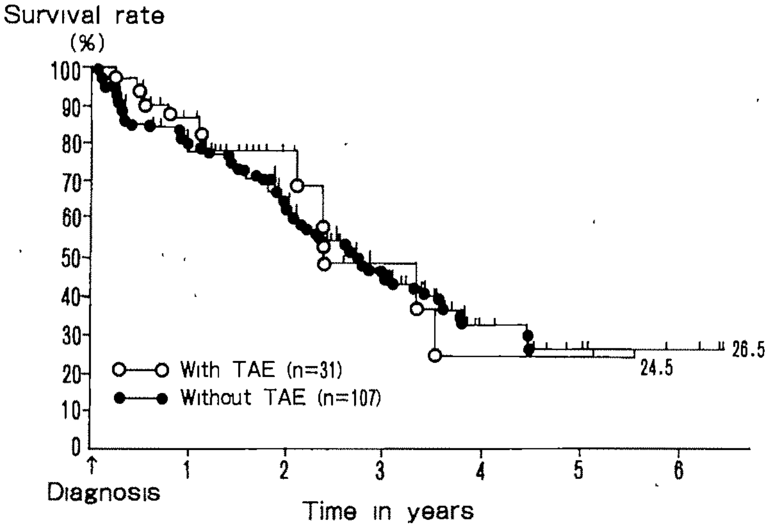

Fig. 2. Cumulative survival rates after diagnosis of HCC in the two study groups No statistical difference was observed.

rate is very high.[3-5, 24] At present, no definitive results are available concerning the role of adjuvant therapy in the treatment of HCC by resection. On the other hand, it seems that TAE of the liver in combination with cytostatic agents has become recognized as one of the best palliative methods for treating nonresectable HCC.[7, 8, 10-19] Although several groups recommend that this method be performed before hepatic resection, even in patients with resectable HCCs,[16-19] none of them has proved scientifically that preoperative TAE is useful in lowering the recurrence rate and prolonging the survival rate. A prospective controlled trial was not used in those studies.

We realize that the weakness of our study was that it was only retrospective. However, we do not assume that our results are invalid. All our patients with preoperative TAE had been treated in other hospitals before they were referred to us. That is, we were not involved at all in deciding whether or not the patient was to undergo embolization. As a result, it is likely that our patients were fairly randomized, and the two study groups were almost homogeneous as shown by the findings of our retrospective comparisons. Among various preoperative data a substantial difference was found only in the time interval between the diagnosis of HCC and surgery. It was significantly longer in the group with TAE. Also results of postoperative histopathologic comparison showed that the type and stage of HCC and underlying liver disease were comparable in the two groups. There were no differences in the extent of liver resection, operation time, and blood loss during surgery. However, various intra-abdominal complications related to TAE were observed in half of the patients who had undergone TAE. In addition, detection of tumor was impossible during surgery, even with ultrasonography, in 5 of 31 patients with TAE. This is a difficult problem in performing minor resection of cirrhotic livers for small, invisible, and unpalpable HCCs.[25]

Despite these intraoperative differences, there were no differences in the postoperative courses of the two groups. The postoperative mortality rate was 13% in the group without TAE and 10% in the group with TAE. Inasmuch as TAE has been used frequently in recent years, the postoperative follow-up time was significantly different; it was shorter in the group with TAE and longer in the group without TAE. Nevertheless, the rate of tumor recurrence in the remnant liver was similar, and the mean time until recurrence was significantly shorter in the patients who underwent embolization. The reason for this is yet to be explained.

When long-term survival of the patients was evaluated, TAE was not found to improve survival. TAE did not produce any beneficial effect in the patients overall and even adversely affected patients with advanced cirrhosis. Results of our study indicate that preoperative TAE is meaningless in the treatment of resectable HCCs and should be avoided, particularly in patients with advanced cirrhosis of the liver. We are now justified in carrying out a prospective study on this subject to determine whether the current provisional results are substantiated.

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Correspondence

C-reactive protein and acute pancreatitis

Sir
Wilson and co-workers have presented data on the value of C-reactive protein, antiproteases and complement factors during the course of acute pancreatitis (*Br J Surg* 1989, **76**: 177–81). They have used the same design as we did some years before[1,2] and their major result is identical with our own, namely 'C-reactive protein is simple, quick to perform, provides useful clinical information and is more likely to be of value and to be adopted into routine clinical practice than multiple factor scoring systems'

In their discussion Wilson and co-workers mention that our data have been based on a study of 35 patients. Obviously, this study population was sufficient to provide comparable information. In addition, the authors mention that the cut-off level of 100 mg/l which we have shown to be predictive for pancreatic necrosis would not be adequate. In our opinion there are two reasons why the authors came to a cut-off level of 210 mg/l for a group of patients with 'severe pancreatitis': (1) they have used another assay system (Abbott TDX, Abbott Laboratories Ltd., Wokingham, Berkshire, UK) to that used in our studies (Laser nephelometry, Behring Werke AG, Marburg, FRG); (2) they have not included contrast-enhanced computed tomography in the diagnostic work-up of their patients with acute pancreatitis. This radiological modality meanwhile has been shown to be the gold standard for the staging of acute pancreatitis[3–6]. We have used this technique in our clinical trials and that is the reason we were able to speak of 'pancreatic necrosis' and why we have set our cut-off level at 100 mg/1. Obviously, the authors have not used this technique and this is one of the reasons why the study population is not comparable to ours and why the authors have based their study on a rather superficial definition of 'severe pancreatitis'.

Finally, the authors mention that our group would have a lower threshold for surgery and that we may be operating unnecessarily in patients with acute pancreatitis. The fact that C-reactive protein has been shown to be a very valuable parameter in indicating pancreatic necrosis has nothing to do with our indication for surgery which is based on clinical criteria such as multiorgan failure or sepsis[7]. Therefore, as we have described in the past, C-reactive protein is more likely to be of value and to be adopted into routine clinical practice than, for example, multiple factor scoring systems; this acute phase reactant does help in the staging of this disease but certainly it does not provide the indication for surgery.

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Authors' reply

Sir
We agree there may be variation in the results from different assays used for the estimation of C-reactive protein but currently there is no evidence that the method we employed (Abbott TDX, Abbott Laboratories Ltd., Wokingham, Berkshire, UK) reports higher values than laser nephelometry (Behring Werke AG, Marburg, FRG) employed by Buchler *et al.*[1] and, if anything, may result in lower values Indeed the overall scatter of C-reactive protein concentrations observed in the two studies appear to be similar. Their cut-off level for C-reactive protein of 100 mg/l for the prediction of 'pancreatic necrosis' remains difficult to explain. Fifty-seven (79 per cent) of our patients would have 'pancreatic necrosis' predicted according to this criterion, but only six came to surgery We have observed high C-reactive protein levels in many patients with mild, uncomplicated pancreatitis (*Figure 5*)[2] and perhaps if they had studied more than 13 of such patients different conclusions regarding the cut-off level may have been reached

With regard to the criteria for surgical intervention, while some of our German colleagues' work makes it clear that clinical, computed tomographic and laboratory criteria are utilized together to aid the decision-making process[3], in other work there is an impression given that serum factors such as C-reactive protein can be employed as specific indicators[1]. It is this latter recommendation which can cause problems

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Biliopancreatic bypass in the Prader–Willi syndrome

Sir
We read with interest the paper by J. J. Brossy (*Br J Surg* 1989, **76**. 313). In his case report, the author states that in patients with the Prader–Willi syndrome 'gastric stapling aggravates the emotional issues' and therefore should not be performed.

We would like to present our experience with a 29-year-old man, showing several clinical features of this syndrome[1] The patient was superobese· height 145 cm, weight 160 kg, body mass index 76 kg/m^2 A gastric bypass (Mason–Griffen modification) was performed The postoperative course was uneventful except for minor wound infection. The patient was dismissed from hospital 25 days after surgery. At the last follow-up (7 months after operation), his weight was 126 kg (a weight reduction of 34 kg), and he had no problems with food intake.

Although long-term results are yet to be assessed we think that a gastric bypass may be an effective treatment of morbid obesity in the Prader–Willi syndrome.

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Leucine kinetics in surgical patients

Sir

Recently published studies by Harrison *et al.* on leucine kinetics in surgical patients (*Br J Surg* 1989; **76**: 505–8 and 509–11) provide a welcome analysis of the conflicting results of studies of whole-body protein metabolism in the context of elective surgery and malignancy respectively. The first paper seems to be a faultless study and analysis, but the second is marred by the fact that the groups reported are too small for firm conclusions to be drawn, although the data can be analysed by the Mann–Whitney *U* test If groups 2, 3 and 4 are taken together and compared with the controls by the same test, the probability that leucine flux is elevated in patients with malignancy is only $P = 0{\cdot}168$ (values estimated from *Figure 1*, page 510). The small group with benign disease and three low values in the group with malignant disease account for this. Inspection of the results reveal that 12 of the 15 values in the group with malignancy lie above the median value for benign disease and six of these are well above the highest value in the controls.

The question that needs to be addressed is why do some individuals with malignant disease have raised leucine flux or nitrogen turnover? There need be no assumption that any effect of malignancy on protein metabolism is related to tumour burden Such an effect, if there is one, may be mediated by a macrophage factor, tumour necrosis factor or cachectin[1] Here an analogy may be made with the effects of interleukin 1 in trauma and sepsis[2]. The presence of a tumour may be sufficient to switch on such a response which may vary between tumours of differing histological types or even between tumours of a similar type This would explain the spread of results within the groups with malignant disease and the variation of results between studies.

The hypothesis that 'host' immune responses to some tumours are responsible for systemic metabolic changes needs to be explored.

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Author's reply

Sir

While we are grateful for Mr H. C. Ward's kind remarks relating to our review of the relevant literature, we find ourselves unable to accept the method he has chosen to criticize our scientific presentation If statistical methods are to serve any purpose it must surely be to encourage the rational and honest examination of the actual data obtained. Asking that the three lowest results are ignored to illustrate a possible trend is as meaningless as suggesting that the three highest results are discounted.

The result of the conventional statistical analysis of our study showed no consistent effect directly attributable to the presence of a colorectal malignant tumour. We would accept that this does not exclude the possibility that there is a subset of patients with such tumours who may have altered nitrogen metabolism. To test such a hypothesis, which we feel should certainly precede any speculation on the pathophysiology involved, would require a different approach, and almost certainly a different methodology, to the one we chose

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Operative mortality after perforated peptic ulcer

Sir

Mr A. B. S. Ball and colleagues are to be congratulated for their paper (*Br J Surg* 1989; **76**: 521–2) which will undoubtedly reawaken interest in the conservative management of perforated duodenal ulcer. Several points are worthy of comment.

Risk factors affecting the outcome in perforated ulcer surgery have been previously documented in a prospective manner[1] It is known that conservative management in the 1950s could produce results comparable to those achieved by surgery today[2]. Our recent prospective randomized trial[3] has adequately confirmed this impression as well as demonstrating that a 12-h period of conservative therapy does not compromise outcome irrespective of further management. Furthermore, adequate protocols exist for the better targeting of selective treatment of patients suffering perforated duodenal ulceration utilizing water-soluble contrast studies during this initial 12-h period[4].

Such foreknowledge can only lead to the better selection of patients likely to benefit from surgery and contribute also to the improved non-surgical management of those who would carry an unreasonable surgical risk.

It should be stressed, however, that the elderly represent a group of patients who localize perforations poorly and although surgery should be avoided if at all possible there should be no undue delay if radiological and clinical evidence of improvement is lacking after 12 h of therapy.

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Contrast-enhanced CT scan in the early phase of acute pancreatitis

Sir

We have read the recent paper by London *et al* (*Br J Surg* 1989, **76** 268–72) with interest and considerable concern. The authors claim that 'pancreatic size index $\geqslant 10\,\text{cm}^2$' (product of pancreatic head and body measurements) represents the simplest computed tomographic (CT) criteria which is applicable to practice, best correlated to the severity of acute pancreatitis, and the 'unique CT parameter for local complications' This index appears over-simplified as great variations exist amongst normal subjects, for instance, young subjects have a larger pancreas than older ones, pancreatic lipomatosis will yield falsely high values and pancreatic atrophy, which is frequent in old and alcoholic patients, will furnish a falsely reassuring index No reference values of pancreatic sizes are given by the investigators CT scanning was not performed on all patients during the study More than half of the deceased patients were not scanned compared with 86 per cent of those with mild pancreatitis; thus excess benign disease was presented, with only six fatal cases! Most other reports[1–3] have exclusively studied severe pancreatitis. Our study[4], although primarily directed at unselected patients contained a slight predominance of the severe form Furthermore, referring to the definition of the disease for their recruitment of patients (serum amylase concentration >3 times the upper reference value) we stress that a significant number of acute pancreatitis patients were underdiagnosed, particularly those of alcoholic origin We recently found that up to 19 per cent of patients with acute pancreatitis had no significant elevation of serum amylase concentration at admission[5]. Regarding this definition and the large number of patients with mild pancreatitis, we do not consider this an unselected study

Finally, the 72 h delay before obtaining computed tomography is too long as the main advantages of early scanning are early confirmation of the diagnosis and prediction of future complications. In our recent prospective study of 202 patients[4], CT scans were performed within 36 h of admission of which 80 per cent were within 24 h. As a result of our investigations, CT had a diagnostic sensitivity of 92 per cent and specificity of 100 per cent. Extrapancreatic spread

(EPS) was found to be of paramount importance in establishing early prognosis and, in this setting, appeared to be of complementary value to clinicobiochemical criteria The type and extension of the oedema correlated to the severity of the disease, and particularly to local complications. In the absence of phlegmonous EPS (i.e. even with the oedematous EPS) the clinical course was mild with no fatalities, whereas in its presence the mortality rate increased to 28 per cent, and exceeded 40 per cent when the phlegmon extended to three or more extrapancreatic areas Arguing the complexity of such grading, London *et al.* have simplified all extrapancreatic manifestations of acute pancreatitis to the 'loss of peripancreatic tissue planes' and, although this later CT criterion had a significant value on the prediction of overall complications ($P = 0\,006$) and was almost significant in predicting local complications ($P = 0\,06$), the authors do not further develop the subject We are also puzzled by the statement that 'contrast-enhanced CT scan adds nothing to a plain scan in establishing the prognosis of acute pancreatitis' This should probably be imputed to the technique of enhancement using slow infusion of contrast media, which often does not allow visualization of pancreatic necrosis, or the differentiation between pancreatic parenchyma and peripancreatic spread (leading to spurious pancreatic measurements[1]), or the differentiation between oedematous and phlegmonous EPS Like others[1–2], we found that rapid-bolus intravenous infusion is mandatory for an optimal enhancement Finally, the renouncement of the Hounsfield units for the evaluation of pancreatic and extrapancreatic enhancement is misleading.

However we agree that routine CT scanning in pancreatitis would be unreasonable and we regret that the authors do not propose situations in which it would be suitable In our opinion, CT scanning is indicated· (1) in all cases of doubtful diagnosis (particularly in the case of normoamylasaemia), (2) in patients presenting some degree of severity in terms of clinicobiochemical criteria (i e. three or more criteria) – the absence of phlegmonous EPS should be reassuring while its presence and extension should alert the clinician of future complications, (3) in all prospective studies A CT scan represents to date the diagnostic 'gold standard' and would allow, in combination with clinicobiochemical criteria, more objective early grading of the severity of the disease

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Switzerland

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2 Kivisaari L, Somer K, Standertskjold-Nordenstam CG, Schroder T, Kivilaakso E, Lempinen M. A new method for the diagnosis of acute haemorrhagic-necrotizing pancreatitis using contrast-enhanced CT scan *Gastrointest Radiol* 1984, 9 27–30
3 Hill MC, Barkin J, Isikoff MB, Silverstein W, Kalser M. Acute pancreatitis clinical *versus* CT findings *AJR* 1982; 139 263–9.
4 Clavien PA, Hauser H, Meyer P, Rohner A Value of contrast-enhanced computerized tomography in the early diagnosis and prognosis of acute pancreatitis A prospective study of 202 patients. *Am J Surg* 1988, 155 457–66
5. Clavien PA, Robert JH, Meyer P, Borst F, Hauser H, Rohner A Acute pancreatitis and normoamylasemia· a not unusual combination. *Ann Surg* 1989 In press

Authors' reply

Sir

We are grateful for the interest that Drs Clavien, Hauser, Meyer and Rohner have shown in our paper We did not claim that a pancreatic size index of $\geqslant 10\,\mathrm{cm}^2$ was a 'unique CT parameter for local complications' but state that we found that this was the CT size index which best predicted the overall severity of pancreatitis As we stated in the paper, we felt that any CT criterion used to predict the severity of pancreatitis should be relatively simple so that it could be applicable to general surgical practice We did not provide normal pancreatic size indices because, of course, for any one patient admitted with established acute pancreatitis there is no way of knowing their normal size index and comparing it with the size index of the inflamed pancreas. It is more relevant to know whether the pancreatic size indices of patients with established pancreatitis can help predict those who will go on to get a severe attack As stated by Dr Clavien and his colleagues the majority of reports concerning the prediction of the severity of acute pancreatitis by computed tomography have exclusively studied patients with severe pancreatitis We intended to scan all patients admitted with acute pancreatitis but for logistic reasons managed to scan 83 per cent There were inevitably relatively more deaths amongst the group of patients who were not scanned because seven patients who were moribund on admission were not referred for CT scanning We feel that this in no way weakens the study because these patients already had a clinically obvious severe attack[1] We included in our study patients with a first attack of pancreatitis and with an amylase concentration > 1000 units/l We note that the incidence of alcoholic aetiology in Dr Clavien's study was twice that in our study and, although during the period of our study a small number of patients with alcoholic pancreatitis were admitted with pain and an amylase concentration < 1000 units/l, none of these patients in our experience has gone on to have a severe attack and we therefore felt that it was not necessary to include them The purpose of this study was specifically to assess the value of computed tomography for the prediction of severity, not the diagnosis of acute pancreatitis.

Dr Clavien and colleagues state that in their study computed tomography had a sensitivity of 92 per cent for the diagnosis of acute pancreatitis, which is the same as our recently published figure[1] Surely it is not possible to produce a figure for the specificity of computed tomography for the diagnosis of acute pancreatitis unless all patients with abdominal pain admitted to an institution have a CT scan? Like Dr Clavien we found that there were highly significant differences in the CT appearances of patients who went on to get mild or severe attacks but we felt that the sensitivity and specificity of these criteria were not good enough to recommend the use of computed tomography in routine clinical practice Dr Clavien does not state the sensitivity or specificity of his various CT criteria for the prediction of severity. It is clearly stated in our paper that our technique for contrast infusion is not comparable with that of Block *et al.*[2] or Kivisaari *et al*[3] who used a rapid-bolus infusion technique in patients with established severe disease to detect pancreatic necrosis.

We did not propose situations in which CT scanning would be suitable because we feel that this needs to be investigated by prospective studies We do not agree that computed tomography represents the diagnostic 'gold-standard' because we have found that 6 per cent of patients with clinically undoubted pancreatitis have normal CT appearances Thus whilst an abnormal CT appearance confirms the diagnosis of acute pancreatitis a normal appearance does not exclude it Whether patients can be selected by biochemical criteria for CT scanning and whether the demonstration of pancreatic necrosis or extra pancreatic spread at an early stage will alter the morbidity or mortality of the disease remain to be determined

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1. London NJM, Neoptolemos JP, Lavelle J, Bailey I, James D Serial computed tomography scanning in acute pancreatitis a prospective study *Gut* 1989, 30 397–403
2 Block S, Maier W, Bittner R, Buchler M, Malfertheiner P, Beger HG Identification of pancreatic necrosis in severe acute pancreatitis imaging procedures *versus* clinical staging *Gut* 1986, 27· 1035–42
3. Kivisaari L, Somer K, Standertskjold-Nordenstam CG, Schroder T, Kivilaakso E, Lempinen M. A new method for the diagnosis of acute haemorrhagic-necrotizing pancreatitis using contrast-enhanced CT. *Gastrointest Radiol* 1984, 9. 27–30

Book reviews

The Foot

B Helal and D. Wilson 80 × 100 mm Pp 1279. Illustrated. 1988 Edinburgh Churchill Livingstone. £150 00

The Foot comes as a pair of heavy volumes with two orthopaedic editors and 62 chapters of expert opinion to show that this surgical Cinderella deserves at least equality with the hand. There is, as one would expect, weighty evidence for the anatomical nicety and functional subtlety of this lowly appendage but also much clinically based material There are excellent reference chapters on weighty subjects such as the mechanics, radiology and surgery, but also useful lighter contributions including mythology, chiropody and the risks of dancing Some chapters are refreshingly analytical There is, for example, a comprehensive review of the controversy between conservative and surgical management in the treatment of rupture of the Achilles' tendon The extremely useful K9, with which at least two surgeons have continued to operate despite being in plaster themselves for this condition, is not included but the review concludes that out of the many trials and reports which have addressed the issue, 'persons who benefit most from operative treatment are high performance athletes' Unhappily, there are also many areas of treatment in which even that degree of certainty is lacking and in some chapters we find authors drawing a variable thickness of literary camouflage over their empirical recommendations.

With admirable logic the work begins with mythology and builds through embryology, anatomy, mechanics and pathology to the climax of treatment Mythology is mentioned again, later, not only in obvious form (half a page on the mythology of the sesamoids in a chapter all their own), but also disguised as expert opinion. The foundation subjects of embryology and anatomy lead on to the complexities of gait, pedobarography and electrodiagnosis, and it is quickly apparent that special investigations are of great value in giving clinical judgement some objective help but that the application of these tests to ordinary practice remains limited. We are a long way from being able to place the foot in a machine and tell its future Forty-five pages are devoted to radiography and radiology and the illustrations of correct positioning and results are detailed and clear A description of local congenital disorders and a lucid and mature appraisal of surgery for myelomeningocele then follow. Those who remember the enthusiasm in the 1960s for early closure of the 'open back lesion' and the suffering of many of the survivors detailed by Lorber in 1971 will welcome this sympathetic but positive account; uncamouflaged empiricism is shown here in the grey but enduring light of reappraisal and the Hunterian surgical experiment bears humane fruit. In the treatment of other neurological disorders conservative neurologists would surely not agree that surgery is wise, for example in peroneal muscular atrophy (Charcot–Marie–Tooth) where relapse is admitted to be 'inevitable', nor in Friedreich's ataxia where it is the ataxia which is disabling and not the neuropathy For many uncommon treatments objective reappraisal is awaited.

If the foot is a Cinderella, what is the status of the great toe? Certainly it now has a worthy champion in Derek Wilson who has contributed 72 pages and 241 references to improve our understanding of hallux valgus and rigidus. Many procedures are listed, suggesting that we are still reaching towards the best. The second volume takes us through tropical diseases in textbook form· brief, clear and informative. Ainhum is described separately, declining to give up its mystery in six pages and also enjoying a second appearance as a skin disorder later on The chapter on diabetes gives firm recommendations for management using the author's flow diagrams and is unashamedly empirical recognizing that the basic metabolic derangement remains obscure The references here give historical perspective but there is no modern discussion on the effect of insulin as opposed to oral hypoglycaemic agents on prognosis and the critical importance of recognizing non-clostridial gas gangrene is understated. The description of vascular assessment is slight and few vascular radiologists or surgeons would now even consider transbrachial arteriography. The role of digital subtraction angiography, although described here as a 'useful tool', has yet to be proved as a better investment than a modern conventional examination with non-ionic media, and neither technique can reliably distinguish embolism from thrombosis as the author implies.

The syndrome of Sudeck's atrophy, reflex sympathetic dystrophy or, to give it Dr Glick's preferred term, Algodystrophy, is mentioned not only in his helpful chapter but also appears in the earlier review of systemic disease by Dr Barnes. This is not the only example of avoidable duplication in the work but is an important one since Dr Barnes covers vascular disease in only one page, and space is required in a work of this authority for a vascular specialist

The editors have been ambitious and in a first edition some overlap in subject matter and variation in terminology is understandable, but for the second edition, which is surely deserved, judicious pruning would permit essential new growth. Updating will also be required, for example to bring the recommendations for support stockings into line with recently approved standards, and to expunge some of the traditional but erroneous views about chemical desloughing, topical antibiotics, penetrating gravitational ulcers and sympathectomy for Raynaud's disease.

Cinderella may now go to the ball confident that if she injures her foot, experts from Messrs Helal and Wilson's book will be on hand to explain how it happened and to restore it to fit the glass slipper she deserves. Meanwhile, the vascular surgeons are still in the kitchen waiting for their invitation from these fairy godmothers

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Operative Ultrasonography. 2nd ed.

B. Sigel. 160 × 240 mm Pp. 231. Illustrated. 1988. New York· Raven Press $86 50.

The publication of the second edition of this book is timely, given the increasing interest being shown in the use of operative ultrasonography. The editor has the stated aim of informing surgeons and radiologists in the use of ultrasonic imaging in the operating room but, despite extensive revision of the first edition, certain key applications of operative ultrasonography are omitted and I was not convinced of its usefulness in some of the areas covered by the book.

The first three chapters give detailed descriptions of the basic principles and general techniques of ultrasonography, although the section on image orientation, outlining experiments using the ultrasound probe in a water tank, could perhaps have been replaced by more detailed description of image orientation with the normal liver, pancreas, kidney, etc

The chapter on the application of operative ultrasonography during liver surgery has been written by two leading exponents of the technique, but this chapter is of little practical benefit to western hepatobiliary surgeons. There is a detailed description on the diagnosis of hepatocellular carcinoma. Detection of associated daughter nodules and tumour thrombi, and a variety of ultrasound-guided hepatic resections are listed. It seems incomprehensible that there is no mention of the use of operative ultrasound in the detection of 'occult' liver metastases in patients undergoing resection of primary gastrointestinal malignancy, and no mention is made of its role in the evaluation and management of hepatic metastases

The chapters on application of operative ultrasonography in biliary and pancreatic surgery are well written, although no mention is made of its use in assessing hilar cholangiocarcinoma. Its usefulness in renal surgery has been diminished with the introduction of lithotripsy but the chapters relating to vascular surgery and neurosurgery were welcome, since its application in these fields seems to be broadening

I suspect that the enthusiastic operative ultrasonographer would buy this book because of the shortage of written material in this field, but both he and the surgeon wishing to learn the technique would be disappointed since the book fails to give sufficient practical information.

D. J. Garden

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Notices and announcements

21–24 August 1989
4th International Symposium on Obesity Surgery
London, UK
Information Mr E R. T C Owen, Academic Surgical Unit, The Queen Elizabeth Queen Mother Wing, St Mary's Hospital, Praed Street, London W2 1NY, UK

6–8 September 1989
4th World Congress of the International Society for Diseases of the Esophagus
Chicago, Illinois, USA
Information: 4th World Congress Coordinator, PO Box 1135, Park Ridge, Illinois 60068, USA

7 September 1989
Paediatric Surgical Research
Graz, Austria
Information: Professor Dr H Sauer, Department of Paediatric Surgery, The University of Graz, Heinrichstrasse 31, A-8010 Graz, Austria

9–10 September 1989
Magnetic Resonance Imaging for Technologists Seminar: A Practical Introduction
Philadelphia, USA
Information· Janice Ford or Nancy Fedullo, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104, USA

10–15 September 1989
3rd International Symposium on Inflammatory Bowel Diseases
Jerusalem, Israel
Information. International Congress and Convention Association, P O. Box 5006, Tel Aviv 61500, Israel

11–16 September 1989
33rd World Congress of Surgery
Toronto, Canada
Information 33rd World Congress of Surgery, Congress Canada, Congress Management, 73 Richmond Street West, Suite 300, Toronto, Canada M5H 1Z4

13–15 September 1989
Association of Anaesthetists of Great Britain and Ireland Annual Scientific Meeting 1989
Swansea, UK
Information· Dr R. S Vaughan, Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA, UK

17–26 September 1989
Frontiers in Gastroenterology: Colorectal Disease
Birmingham, UK
Information. Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

19–20 September 1989
New Trends in Pelvic Pouch Procedures
Bologna, Italy
Information: R. M Società di Congressi srl, Via Ciro Menotti 11–20129, Milano, Italy

21–23 September 1989
Annual General Meeting of the Association of Surgeons in Training
Cardiff, Wales, UK
Information· Mr B J. Harrison, Department of Surgery, Cardiff Royal Infirmary, Newport Road, Cardiff CF2 1SZ, UK

22–24 September 1989
Association of Colon and Rectal Surgeons of India
Soura Sringar, India
Information. Dr N. A Wani, Organizing Secretary, Room No 1318, Sher-i-Kashmir Institute of Medical Sciences, Soura Srinagar, India

22–25 September 1989
58th Annual Meeting of the Royal College of Physicians and Surgeons of Canada
Edmonton, Canada
Information· Anna Lee Chabot, Head of the Meetings and Assemblies Section, Office of Fellowship Affairs, The Royal College of Physicians and Surgeons of Canada, 74 Stanley, Ottawa, Canada K1M 1P4

27–29 September 1989
British Society of Gastroenterology Autumn Meeting
Dublin, Ireland
Information. Charles Fletcher, Confrex, P.O Box 963, Brighton, East Sussex BN1 6TN, UK

27 September–1 October 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Information· The Secretariat, 2nd International Conference on Gastrointestinal Cancer, P O Box 50006, Tel Aviv 61500, Israel

4–7 October 1989
Principles of Colon and Rectal Surgery
Minneapolis, USA
Information Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast , Minneapolis, Minnesota 55455, USA

5–7 October 1989
2nd International Tissue Expansion Symposium
Marseille, France
Information Sud Congres Services, 4 bis, Impasse du Roc-Fleuri, 1300 Marseille, France

15–20 October 1989
American College of Surgeons 1989 Annual Clinical Congress
Atlanta, USA
Information Sally Garneski or Susan Krasnow, American College of Surgeons, 55 East Erie Street, Chicago, Illinois, USA

15–21 October 1989
Recent Advances in Pancreaticobiliary Surgery
Edinburgh, UK
Information Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

16–20 October 1989
Sixth World Congress on Medical Informatics MEDINFO 89
Beijing, China
Information. Dr Phil R. Manning, Chairman, Scientific Programme Committee, MEDINFO 89, USC School of Medicine, 1975 Zonal Avenue, KAM 317, Los Angeles, California 90033, USA

6 November 1989
How to write a Surgical Paper
London, UK
Information Mary Wheaton, Hunterian Institute Office, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information· J P. Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

23–24 November 1989
Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland
Dundee, UK
Information. Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

3–9 December 1989
Breast Cancer: New Developments in Biology, Diagnosis and Treatment
UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information. Dr Joseph W C Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

20–21 January 1989
Hong Kong Surgical Forum
Hong Kong
Information. Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

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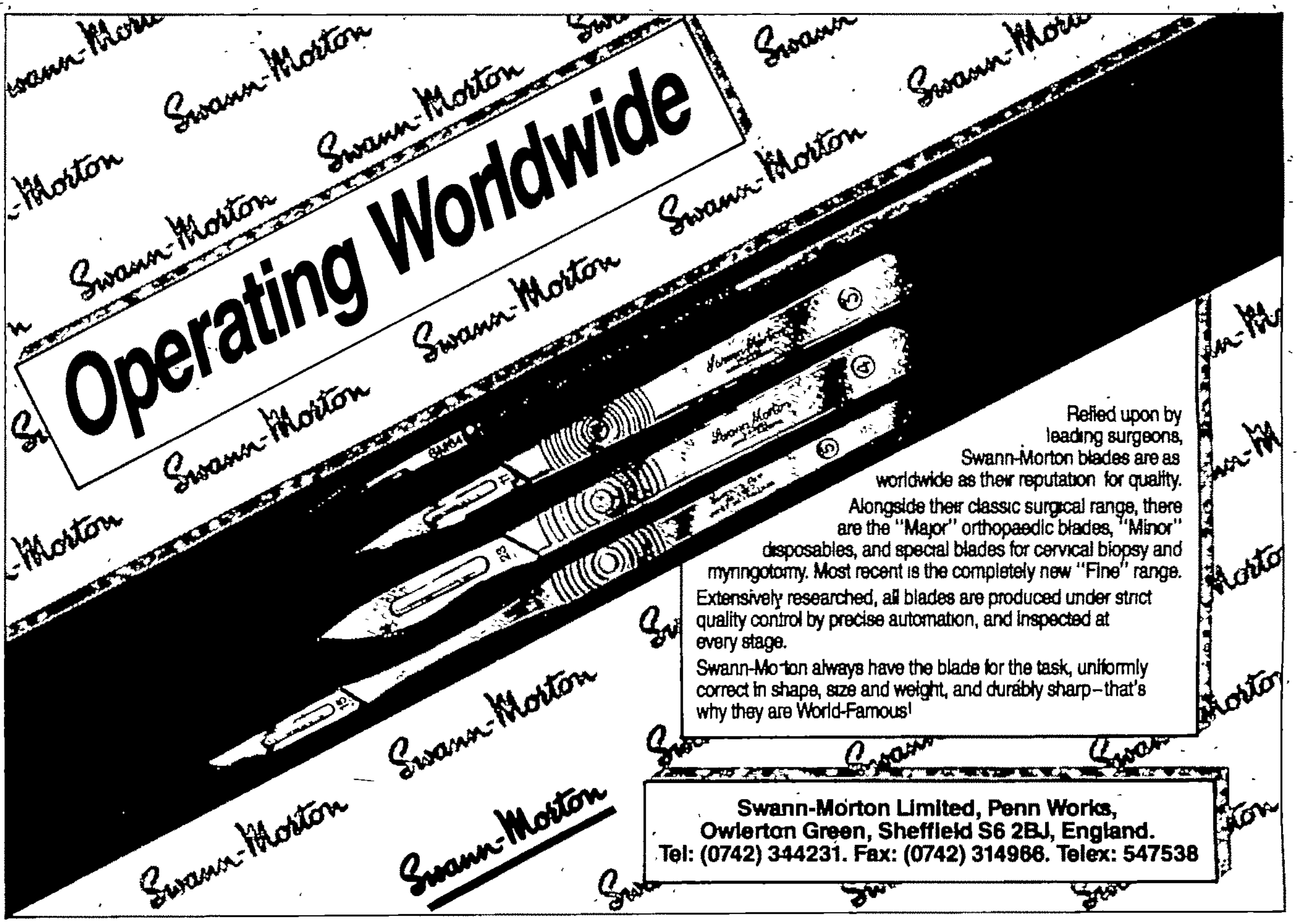

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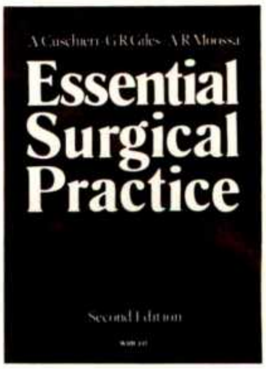

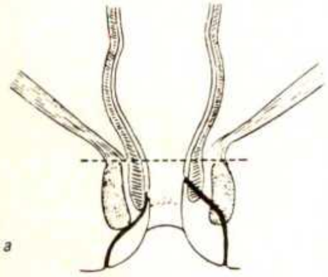

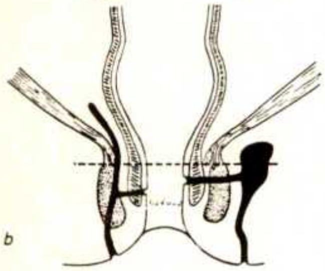

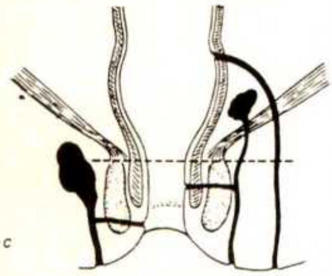

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Management of ingrowing toenail

Fourteen years ago this journal published my first paper: a review of the management of 200 patients who attended the Western Infirmary, Glasgow, between 1966 and 1970 with a diagnosis of ingrowing toenail[1]. Avulsion of the hallux nail was the most common treatment recorded (72 per cent) with 35 per cent of these patients having more than one avulsion at the same site. General anaesthesia was used for 30 per cent of hallux nail avulsions. Recurrence of ingrowing toenail occurred in 64 per cent of the patients after the first avulsion and 80 per cent after subsequent avulsions. The most common surgical procedure used to treat ingrowing toenail was total proximal nailbed ablation as described by Zadik[2] General anaesthesia was employed for 97 per cent of these procedures and a 16 per cent symptomatic recurrence rate was noted. The paper recommended that local analgesia be used for the vast majority of hallux nail avulsions and nailbed ablation procedures. A management protocol was outlined that advocated nail avulsion at the first hospital presentation; this was backed up with advice to the patient on care of the new hallux nail during regrowth. Nailbed ablation using the Zadik technique was recommended for any postavulsion recurrence of ingrowing toenail. In writing this article I have reassessed my 1975 management protocol for ingrowing toenail and attempted to highlight the changes in management that have occurred over the last 14 years.

Conservative treatment of ingrowing toenail has never been popular with surgeons. This form of management is time consuming, demands a high level of patient co-operation and requires patience from both doctor and patient. There is no doubt, however, that conservative treatment of ingrowing toenail can be successful, especially in young adults with early disease and a non-dystrophic nail. This was well illustrated in 1963 by Lloyd-Davis and Brill[3], who reported that 60 per cent of the patients attending their toe clinic at St. Thomas' Hospital, London, with ingrowing toenail were cured by, or were responding well to, conservative treatment. The article by Reijnen and Goris[4] in this issue supports a role for conservative treatment of ingrowing toenail. The authors report a high initial success rate (96 per cent) for conservative management in young patients with early disease but admit to a lower success rate and higher recurrence rate when managing chronic ingrowing toenail conservatively.

Arguably the most significant advance in the efficiency of surgical management of ingrowing toenail over the last two decades has been the acceptance that the vast majority of patients can be treated using local analgesia rather than general anaesthesia. The ring block technique employing a 50:50 mixture of 2 per cent plain lignocaine and 0·5 per cent bupivacaine gives excellent analgesia starting within a few minutes of injection and lasting for 6–8 h by which time most patients are settled comfortably at home. This technique should be mastered by all trainees in general surgery.

The use of hallux nail avulsion to treat ingrowing toenail has declined significantly over the last 14 years. Most surgeons are unhappy to accept a recurrence rate of over 50 per cent and are aware of the difficulties associated with optimal care of the regrowing nail. Nailbed ablation using phenol has removed the need to avulse the hallux nail to eradicate sepsis before excision ablation of the nailbed, and this advance has further limited the use of hallux nail avulsion. Simple avulsion should now be confined to the urgent situation in an accident and emergency department where severe pain from ingrowing toenail requires treatment in the absence of expertise to carry out a definitive procedure.

Publications over the last 14 years have confirmed that nailbed ablation using phenol as described by Ross in 1969 (Reference 5) is superior to nailbed excision techniques as described by Winograd[6], and Zadik[2]. Phenol cauterization of the nailbed is preferred by patients and is associated with a lower nail regrowth rate than nailbed excision[7–11]. Ramsay and Caldwell[10] report a 3 per cent recurrence rate from 1013 phenol cauterizations followed for 12 months, while Young and Rutherford[12] report a 7 per cent recurrence rate occurring within 1 year in 60 patients followed for 3 years. Technique is important and attention must be paid to details outlined in the literature. Haemostatis is essential during phenolization as

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blood effectively neutralizes phenol cautery. Phenol must be carefully applied because cautery of tissue other than the nailbed increases morbidity and can result in litigation.

Phenolization of the whole proximal nailbed has been commonly used to treat ingrowing toenail. This technique remains appropriate for the management of onychogryphosis and other conditions involving significant nail dystrophia. For true ingrowing toenail, however, it has become apparent that at least the central one-third of the hallux nail should be left and phenolization should be restricted to one or both edges (25–30 per cent on each side) of the nailbed depending on presentation. The splinting effect of the residual nail improves the resultant shape of the hallux. This is more cosmetically acceptable and avoids the risk of hyperkeratosis of the exposed nailbed[10].

For me, the last 14 years have helped to simplify the management of ingrowing toenail. Clinical studies have identified what each procedure has to offer and the options now appear clearly defined. Conservative management may abort some early cases but this form of care calls for interest and expertise[4] and is best delivered at a toe clinic staffed by a chiropodist and a surgeon. Partial phenolization should be offered for established ingrowing toenail and should be carried out by surgeons who have received appropriate training. Patient review after 6 months will provide a useful audit of technical performance.

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Selection of patients for breast conservation

That some breast cancers may be safely treated by less than mastectomy is now widely accepted; however, the rules that should govern the choice of patients for this conservative management vary from centre to centre because there is not yet a sufficient body of information on which general principles could confidently be based. Two papers published in this issue of the journal (pages 890–894 and pages 898–900) address the difficult problem of local recurrence after conservative surgery; both show a substantial incidence. In the study from Birmingham the figure was 35 per cent at a mean follow-up of 47 months in a series of mainly elderly patients where surgery had not been followed by radiotherapy. In the series of much younger patients from Nottingham the rate of local recurrence in the breast was 21 per cent. These figures are at the high end of the reported range, the low end of which is in single figures. Zealous conservationists may dismiss these high incidences as due to over-generous selection of patients or flawed surgical or radiotherapeutic technique. By contrast, the diminishing band of unflinching mastectomists may take the figures as confirming their prejudices against any treatment short of mastectomy. The papers should, however, be viewed as stages in the current difficult but crucial process of defining the proper indications for and strategies of conservation.

When all the evidence is taken into account it seems that youth, a large tumour, vascular or lymphatic invasion, extensive surrounding *in situ* disease, regional lymph node involvement, a high grade tumour and negative oestrogen receptor status may all be separately and interactively related to local recurrence after conservative treatment, just as they are after total mastectomy. Local recurrence is on balance commoner after conservation than after mastectomy but arguably is easier to treat. Whether mastectomy after recurrence in the retained breast carries a penalty of a greater risk of mortality than if mastectomy had been the original treatment remains to be shown. Additionally, it is clear that conservation does not necessarily yield a happier woman than does mastectomy. Thus many questions about the application of breast conservation remain to be answered and it is crucial in the mean time that the practice of breast conservation should be attended by the utmost prudence in selection, care in technique and penetrating pathological and clinical review of long-term as well as short-term outcomes.

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Personal comment

The English Surgeon Abroad

Every 2 years there is a meeting entitled the International Surgical Week, hosted by the International Society of Surgery, International Association of Endocrine Surgeons and the International College of Digestive Surgeons, with at least 13 other participating societies or associations. It is a meeting that attracts 3000 surgeons from around the world and has a deservedly high reputation for the quality of its papers, panels and symposia. Some years ago the International Society of Surgeons (originally christened the Société International de Chirurgie) decided that English was to be its *lingua franca scientifica*. All papers are now given in English with no simultaneous translation. Why then is it that so few British surgeons attend these meetings and, in particular, why do so few submit papers for presentation? The number of authors submitting papers for the Toronto conference in 1989 is shown in the *Table*. The Japanese lead the table with 202 authors submitting at least one paper, the West Germans have 135, the USA 110, Italy 64 and Canada (the host country) has 50. The UK's 12th place is behind the USSR and Spain and behind such small population countries as Sweden, Switzerland and Greece.

	Number of authors who submitted one or more papers	Number of panel moderators invited by scientific committee	Number of panel members chosen by scientific committee
Japan	202	0	5
FRG	135	0	10
USA	110	4	23
Italy	64	1	7
Canada	50	3	8
France	42	0	8
Sweden	36	2	5
USSR	31	0	0
Spain	30	0	1
Greece	27	0	0
Switzerland	22	1	2
UK	21	5	10
Austria	21	0	0

What are the reasons for such poor British participation? Is it because of poverty, arrogance or apathy? It could be argued that the Swedes are financially subsidized to attend such meetings and that there are at least 64 rich general surgeons in Italy. However, it is unlikely that the average consultant surgeon in the UK is worse off than the average consultant in Spain, Greece or Italy. Arrogance is always a possible motive for the stay-away British; it is possible that they consider that they have such high quality regional and national meetings that there is no need to find out what the rest of the world is doing or thinking However, it is more likely that apathy rather than poverty is the principal reason why they stay away from international meetings. Perhaps it is apathy engendered by too long a training.

Despite the poor British attendance and free paper submission, the rest of the world seems to regard British surgery highly for, of the 16 panel moderators chosen for the Toronto meeting, the largest number (five) come from the UK, one more than from the USA and two more than from Canada. It is possible that the British tend to be chosen to be moderators because of their ability to be understood clearly by most of the rest of the world for whom English is only their second language. Perhaps it is because they mutilate the English language less blatantly than do those from the USA. Surely we must acknowledge that it is only recognized world experts who will be selected as panel participants. It is interesting therefore to consider the distribution of the 79 chosen panelists for the major sessions in Toronto. The UK, with ten, is equal second with West Germany in the league table, not far behind the 23 panelists from the leading nation, the USA.

It is dangerous to draw too many conclusions from these data but it does seem that much of the rest of the world tends to regard highly British surgery or at least some British surgeons. The poor overall submission rate for free papers and poor attendance of British surgeons in general is, I believe, most likely to be related to apathy; possibly the consequence of our over- long period of surgical training. From the time that a British surgeon starts his specialist training, it is between 10 and 16 years before he or she achieves a definitive consultant post. Once a consultant post has been achieved, the appointees are safe and almost 'fire-proof'. Are they also worn out and apathetic as a result of over-training? It will be interesting to see whether the promised alteration in the promotion structure in British surgery makes any difference to British participation in international meetings.

British surgeons have always had a tendency to think of themselves as of the elite; it comes of something of a surprise to me to find that other nations still show a tendency to rate the best British surgeons quite highly.

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Typhoid perforation

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Typhoid perforation of the bowel carries a high risk of mortality and is a common surgical problem in many developing countries. This review examines the pathogenesis, and discusses diagnosis and management.

Keywords: Typhoid perforation, diagnosis, management

Perforation of the bowel is the most serious complication of typhoid fever, and remains a significant surgical problem in many parts of the world[1–5]. It is traditionally associated with a high mortality, not least because it occurs most commonly in areas where optimal medical care is not readily available

It is now generally accepted that the best definitive treatment is surgical[1–3,6,7], and few would now advocate conservative management[8,9]. However, there is no general agreement about the best surgical procedure, and many have been recommended[2,5,6,10,11]. This has often led to less emphasis being placed on the other essential therapeutic measures; aggressive fluid and electrolyte therapy, blood transfusion and antibiotics will all help to reduce mortality[3,7,12].

Pathology

Typhoid fever is caused by *Salmonella typhi*, a Gram-negative bacillus, and is acquired by ingestion of contaminated water or food. The disease has a seasonal incidence, peaking at times of heavy rainfall, when water contamination is more likely[7]. The organism passes through Peyer's patches without causing inflammation. Multiplication occurs in the reticuloendothelial system during an incubation period of 10–14 days. Seeding into the bloodstream corresponds to clinical onset, and during the second week of symptomatic illness the bacteria reach the gut, either via the bile or by bacteraemic spread, and localize in Peyer's patches. Ulceration occurs and there is an associated mesenteric adenitis The main inflammatory cells involved in this phase are macrophages; some lymphocytes are also present, but polymorphonuclear leucocytes are almost completely absent[13]. It has been postulated that much of the damage done may be due to the body's response to the organism (the mononuclear cell response is characteristic of delayed hypersensitivity). This may help to explain the fact that perforation is known to occur also in patients already on anti-*Salmonella* treatment[7].

Macroscopically, Peyer's patches will be seen to be swollen, red and raised, and solitary lymphoid follicles are also affected The mesenteric nodes are enlarged The terminal ileum and caecum are involved, and the appendix may be inflamed. Ulceration with haemorrhage may occur, as may perforation. The ulceration occurs in the long axis of the bowel, and where perforation does not occur and the disease subsides healing occurs without scarring, so that late strictures are not seen. Perforation occurs classically on the antimesenteric border of the terminal ileum[10,12]. Caecal perforation can also occur but is far less common. In about 20 per cent of cases multiple perforations are present[1,7]. The size of the perforation varies, but true microperforations are uncommon and the average diameter[10] is 5 mm. Although this complication may occur earlier[7], it usually occurs in the second week of clinical illness, the average length of the history being 8–11 days[1,10].

The incidence of bowel perforation in typhoid fever varies markedly from place to place and also appears to be changing with time[3,10,14], the highest quoted incidence being from Ghana (17·9 per cent)[7]. Typhoid perforation is commoner in men and in those under 40 years of age[2,4,7].

Diagnosis

Typhoid fever is characterized by fever (which ranges from 38·5 to 40°C), splenomegaly (by the end of the first week) and the appearance of Rose spots (which are difficult to see in deeply pigmented peoples). Rose spots occur in less than 50 per cent of cases, typically on the upper abdomen, and fade in hours or days. Other features include headache, respiratory complaints and relative bradycardia. Constipation may be the predominant feature in a significant proportion of cases, and diarrhoea is not uncommon, especially in children. Abdominal pain may also be a feature, and mental confusion is not unusual Complications include pneumonia, gastrointestinal bleeding, perforation, cholecystitis, cystitis and osteomyelitis. The white blood count is normal or low, with neutropenia. Anaemia is common and often multifactorial. Definitive diagnosis is made by culture of the organism from the blood (weeks 1 and 2), urine or faeces (from the second week on). A rising titre of agglutinin (the Widal test) is usually diagnostic (towards the end of the second week), but a single test may mislead, especially if the patient has had previous TAB vaccination. The differential diagnosis includes malaria, respiratory and urinary infections, viral fevers, meningitis, occult abscess and endocarditis.

The diagnosis of perforation is suggested by increasing abdominal pain, often beginning in the right iliac fossa or lower abdomen and spreading from there. The most helpful clinical signs are tenderness, rigidity, guarding and loss of liver dullness[3]. Free subdiaphragmatic gas is present in up to 75 per cent of cases[7]. The white cell count is not helpful, as it may be normal, low or high[1,3]. The differential diagnosis at this stage includes perforated peptic ulcer and perforated appendicitis, as well as late intestinal obstruction and other causes of ileus, but the preceding history of fever (usually for more than 1 week) and other clinical features of typhoid will usually point to the correct diagnosis. The necessity for prompt surgery precludes confirming the diagnosis of typhoid preoperatively by cultures or by Widal's test.

It is well to remember that the classical signs of perforation may be absent in those who are very toxic, and repeated abdominal examination is stressed by several authors[7,10]. Most clinical difficulty arises in patients known or considered to have typhoid who have abdominal symptoms but equivocal signs and no free subdiaphragmatic gas on X-ray If doubt persists despite repeated clinical examination, exploration is better than continued observation

Management of typhoid perforation

General management

A full blood count, sickle cell test, urea and electrolyte measurement, and urinalysis should be performed, and a nasogastric tube passed. Dehydration is common In addition

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to having peritonitis, most of these patients have been ill and febrile for a week or more. Fluid and electrolyte replacement should be aggressive, based on clinical findings (blood pressure, pulse rate, degree of clinical dehydration), laboratory findings and response to treatment (urine output should be at least 30–40 ml/h). Correction of blood gas abnormalities and central venous pressure monitoring may be useful in severe cases but are not always possible. Anaemia is common[3,7] and may be partially masked by dehydration. Transfusion is often indicated, but is seldom a top priority in resuscitation.

Many drugs are effective against *S. typhi*, and effective agents include chloramphenicol, amoxycillin, ampicillin, co-trimoxazole and trimethoprim[14]. Chloramphenicol remains the drug of first choice, and is given in an initial dose of 500 mg 4-hourly intravenously in adults (or 50 mg/kg per day). Drug resistance has been encountered and, particularly in epidemics, every effort should be made to establish the drug sensitivity of the organism as soon as possible. If doubt exists a combination of chloramphenicol and amoxycillin or ampicillin is recommended. In perforation, the regimen must include drugs effective against the common enteric organisms, including anaerobes. In practice a combination of chloramphenicol, ampicillin and metronidazole is often used.

Most patients will be resuscitated sufficiently within a few hours to withstand surgery, but a few, usually those with long-standing perforation or those with coexisting disease, will be so severely ill that it may be felt that they are not fit for anaesthesia. Here the clinician must make the final decision, with the reminder that surgery does offer the best hope for survival.

Surgical management

Most authors recommend surgery[1–3,6,7], and few advocates of conservative management remain[8,9]. Many series of patients managed conservatively show mortality rates of over 60 per cent[2,3]. Some authors have pointed out that from time to time the diagnosis will be wrong, but that a perforated peptic ulcer or perforated appendix may be found, and that this is an additional reason for advocating surgery[7,12].

Exploration is usually carried out through a right paramedian incision. An alternative in children is the McBurney or gridiron incision. The risks of subsequent wound dehiscence are greatly reduced, but access for thorough peritoneal toilet is less good and there are theoretical objections to using a gridiron incision in cases where the appendix is left *in situ*.

A thorough laparotomy is carried out, with particular attention being paid to the possibility of multiple perforations, and to excluding areas of localized pus in long-standing cases.

The exact surgical management of the perforation remains controversial, and the following methods are some that have found favour: simple closure[3,6,7,10,12], ulcer excision and closure[15], wedge excision and closure[1], ileal resection and anastomosis, resection and ileotransverse colostomy[2], and right hemicolectomy. In solitary perforations, simple closure with or without ulcer excision remains unchallenged as the procedure of choice[15,16]. Closure should be in two layers, an inner layer of chromic catgut and an outer layer of silk, with the hole being closed in a transverse direction to avoid narrowing the bowel. Multiple perforations pose greater problems, and bowel resection is probably advisable if three or more perforations are present[5]. Right hemicolectomy is only justified in cases of caecal perforation. Regardless of other treatments, any areas of apparent impending perforation should also be oversewn[2,15].

Thorough peritoneal lavage is then carried out with copious amounts of warmed normal saline. Although classically one or more drains have been used in these patients, present knowledge suggests that these may be safely dispensed with. The skin is left open to reduce the incidence and severity of wound infection, and consideration should be given to the use of two or three tension-relieving sutures to minimize the risk of wound dehiscence.

The incidence of postoperative complications is high. Respiratory infections, anaemia and wound infection are all common, and management is often made more difficult by the development of toxic confusional states[2,7,11]. Reperforation or new perforation is possible, and if the diagnosis is suspected against a background of a very ill patient recovering from generalized peritonitis, perhaps with established paralytic ileus, then reoperation is indicated. The mortality rate is high but death is not inevitable. Other major complications include faecal fistula, wound dehiscence and intra-abdominal abscess.

Mortality

The mortality rates from typhoid perforation vary widely in reported series, the range being about 10–60 per cent. Excluding those managed medically, a variety of factors are known to be associated with a higher mortality rate, including late presentation[3,7], female sex[5,7], age over 40 years[7,17], and presence of multiple perforations[5].

Typhoid perforation is now mainly a disease of the developing world, and the medical facilities available for the management of these patients are often less than ideal. It is not surprising that mortality rates vary so widely from place to place. The importance of making the patient fit for surgery cannot be over-emphasized, and in one study[15] an average of 10 h was spent in preoperative resuscitation.

Aftercare

Antityphoid treatment should be continued for at least 14 days If relapse occurs it usually responds promptly to the standard drugs. Instruction with regard to personal hygiene and disposal of faeces and urine is important, as some patients can continue to excrete the organisms for many months afterwards

Long-term complications of surgery include adhesions and obstruction, and incisional hernia. In the few patients in whom terminal ileal resection has been carried out, vitamin B_{12} supplements are necessary.

Conclusion

Ultimately the problem is one that should be solved by public health measures such as the provision of a clean water supply, safe disposal of sewage and instruction in personal hygiene The fact that the organism depends for its continued survival on human-to-human contact makes control measures, if properly applied, more likely to be effective. Prevention by vaccination is incomplete, and impractical in areas where the disease is endemic, but will be useful in localized epidemics.

Meanwhile much can be done to lower to a minimum the risk of mortality in patients with established perforation. Early patient presentation is important, and aggressive initial management with intravenous fluids, antibiotics, blood transfusion and prompt surgery, with careful closure of the perforation, should result in fewer deaths from this dangerous condition

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Factors influencing local recurrence after excision and radiotherapy for primary breast cancer

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Between November 1979 and December 1986, 263 patients were treated for primary breast cancer by local excision and radiotherapy at the City Hospital, Nottingham. Local recurrence within the treated breast occurred in 56 patients (21 per cent), in 18 (6·8 per cent) of whom it was gross and uncontrollable. An analysis of clinicopathological features shows patient age, nodal status, tumour size, presence of definitive vascular invasion, adjacent ductal carcinoma in situ *and grade to be predictive of local recurrence. A Cox's multivariate analysis of these factors shows the first four to be independently significant. The factors can be combined as a prognostic index which allows identification of patients at high risk of local recurrence. On the basis of these findings we have altered our selection policy for patients suitable for breast conservation.*

Keywords: Breast cancer, breast conservation, radiotherapy, recurrence

Breast conservation treatment by local excision and radiotherapy is increasingly used for primary breast cancer. In Nottingham this treatment has been practised for 9 years. A significant proportion of patients have suffered local recurrence, which we have defined as recurrence in the skin or parenchyma of the treated breast. A number of these have been extensive and uncontrollable. The purpose of this study was to evaluate the extent of this problem, to determine which clinicopathological factors predisposed patients to local recurrence and, based on this knowledge, to redefine our selection policy for primary excision and radiotherapy for breast cancer.

Patients and methods

Primary excision with radiotherapy has been a treatment option offered to patients with breast cancer in Nottingham since 1979. Patient choice has always been an important consideration in planning treatment. Patients with operable breast cancers are counselled by a trained counselling sister and offered a choice between simple and subcutaneous mastectomy or excision and radiotherapy. For the latter treatment the initial criteria were that the tumour should be ≤5·0 cm diameter clinically, should not involve the skin or nipple and should not be deeply fixed.

The operative technique was to obtain macroscopic tumour excision. All patients underwent double node biopsy for prognostic purposes[1] at, or shortly after, the time of tumour excision: one node was sampled from low in the axilla and one from the internal mammary chain via the second interspace.

After surgery patients received whole breast irradiation of 45 Gy and a 15 Gy booster to the tumour bed using a 4 or 6 Mv linear accelerator, over 6 weeks. Build up was not routinely used

A strict follow-up protocol was observed for all patients with 3-monthly review for 24 months, 6-monthly review to 5 years and thereafter annual follow-up. Patients received treated-breast mammography 6-monthly for 2 years and then annually. Only patients likely to have a good prognosis had annual opposite breast mammography.

Age, tumour size and nodal status were recorded prospectively in all patients Tumour size was measured by taking the maximum dimension in the fresh bisected specimen The histopathological grade (based on Elston's modification of the Bloom and Richardson method[2]) was assessed in 253 patients, the remaining ten had ductal carcinoma *in situ* without evidence of invasion and were not graded. Completeness of surgical excision was determined by the proximity of the tumour to the surgically cut edge of the specimen. Initially in the series this was not routinely recorded but latterly it has been recorded as complete, close or incomplete Some other factors have been assessed retrospectively by one pathologist (I.O.E): vascular invasion was defined as the presence of tumour cells in lymphatic or venous spaces within or adjacent to the primary tumour and was scored as present, suspicious or absent, the presence of ductal carcinoma *in situ* adjacent to the invasive tumour was assessed by dividing the microscopic field into four quadrants, determining the presence of carcinoma in each quadrant and scoring the adjacent ductal carcinoma *in situ* on a scale from 0 to 4. The ten patients with ductal carcinoma *in situ* and no invasive tumour were all scored 4. These patients were included as three suffered local recurrence, one with invasive carcinoma.

The contribution of these factors to subsequent local recurrence has been investigated by means of Mantel's life table method A Cox's mutivariate analysis was used to determine which, if any, factors measured were independent predictors of local recurrence within the breast

Results

Between November 1979 and December 1986, 263 patients underwent excision and radiotherapy for primary breast cancer at the City Hospital, Nottingham. The median age of the group was 42 years (range 23–69 years, 95 per cent confidence limits 41 to 43 years). The results were analysed in January 1988 giving a minimum follow-up of 12 months.

Fifty-six patients (21 per cent) have suffered local recurrence in the treated breast. Previously it has been reported from this unit[3] that 68 of 405 patients (16·8 per cent) developed flap recurrence after simple mastectomy and a similar duration of follow-up. The types of local recurrence are seen in *Table 1*. In five patients the recurrence was in the form of a skin nodule and was dealt with by further local excision. In eight of the 35 patients whose recurrence was manifest as a breast lump the tumour developed into uncontrollable local disease despite mastectomy. A further ten patients presented with the treated breast parenchyma (and/or skin) diffusely involved with recurrent tumour; these patients had uncontrollable local disease.

Table 1 *Local recurrence in the treated breast*

Presenting type of recurrence	Number
Skin nodule	5
Breast lump	35
Field change	10
Impalpable, mammographically detected	6

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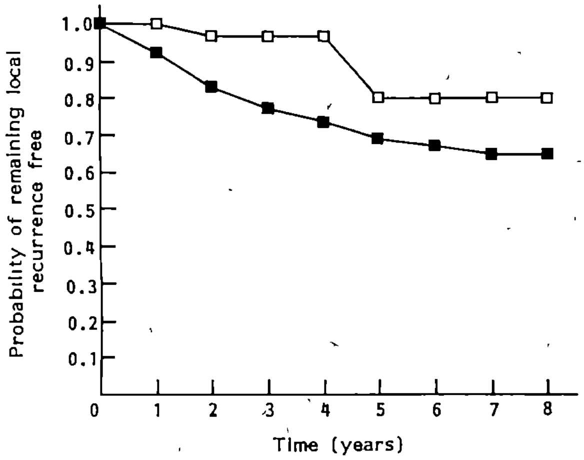
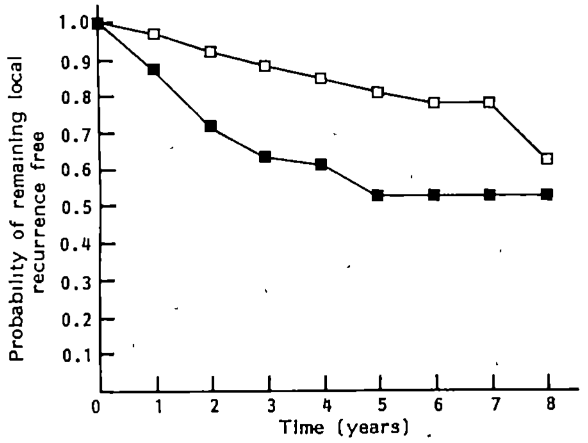
Table 2 *Clinical status of patients at diagnosis of local recurrence*

Clinical status	Number
No evidence of nodal or metastatic spread	33
Concurrent or prior ipsilateral nodal involvement	14
Concurrent or prior ipsilateral nodal involvement and distant metastases	8
Distant metastases only	1



Number at risk									
□	38	36	18	11	8	3	2	0
■	225	196	143	106	80	42	31	15

Figure 1 *Patient age* versus *local rcurrence·* □, *patients* ≥ 50 *years old;* ■, *patients* <50 *years old,* $\chi^2=4{\cdot}17(1\ d.f.)$, $P<0\ 05$ *The number of patients at risk during each time period is given*



Number at risk									
□	174	161	112	82	62	31	20	9
■	89	71	49	35	26	14	13	7

Figure 2 *Tumour size* versus *local recurrence.* □, *tumour size* $\leq 2\ 0$ *cm;* ■, *tumour size* $>2{\cdot}0$ *cm,* $\chi^2=17{\cdot}1(1\ d.f.)$, $P<0{\cdot}001$ *The number of patients at risk during each time period is given*

Thus, 18 patients (6·8 per cent) have suffered uncontrollable local disease. Of these 18 patients, 15 developed distant metastases, six before or at the time of diagnosis of local recurrence and nine developed them between 1 and 11 months after local recurrence.

Fifty-nine patients developed ipsilateral nodal recurrence; 27 of these also had local recurrence. Thus 32 patients had ipsilateral nodal recurrence alone. Combining breast and nodal recurrence gives an overall rate of 88 out of 263 (33 per cent). The clinical status of the patients at diagnosis of local recurrence is detailed in *Table 2*.

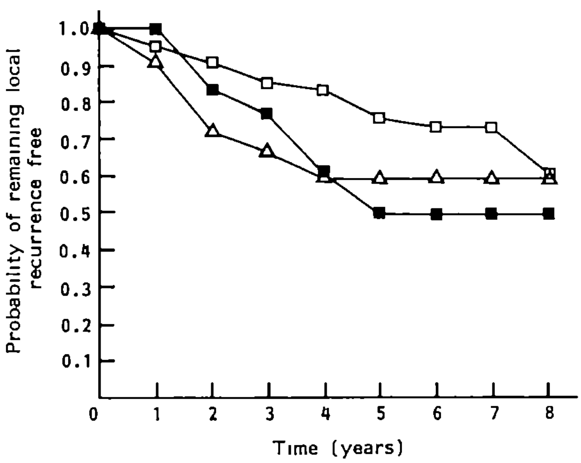
In 36 patients local recurrence was at the same site as the original tumour, in ten recurrence was elsewhere in the breast and ten had diffuse breast involvement.

The influence of the recorded variables on subsequent local recurrence is seen in *Figures 1–7*. Except for completeness of surgical excision, all variables reach statistical significance. The results of the Cox multivariate analysis are shown in *Table 3*. A z value $\geq 1{\cdot}96$ indicates the variable has independent significance. The B value indicates the relative power of each of these variables. As can be seen from *Table 3* four factors have emerged as significant independent variables namely vascular invasion, tumour size, patient age and lymph node stage. Using the B values a prognostic index has been constructed, in the same way that this unit has previously developed a prognostic index for primary breast cancer[4]. Index = (0·7 × vascular invasion) + (0·4 × stage) + (0·25 × tumour size) − (0·06 × patient age).

This index has been calculated for each patient in the study. The indices of the four quartile groups are: 1 = −2·5 to −1·04; 2 = −1·0 to −0·51; 3 = −0·5 to 0·33; and 4 = >0·33.

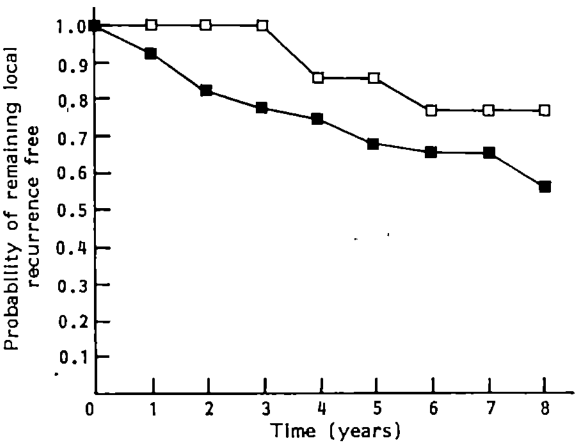
Using these four groups, life-table analysis of the probability of local recurrence within each has been determined and is shown in *Figure 8*. The 65 patients in prognostic group 4 had a 55 per cent risk of local recurrence at 8 years; the 66 patients in group 1 had an 11 per cent risk of local recurrence at 8 years.

To simplify matters further and give a more usable index we have also constructed actuarial curves for local recurrence



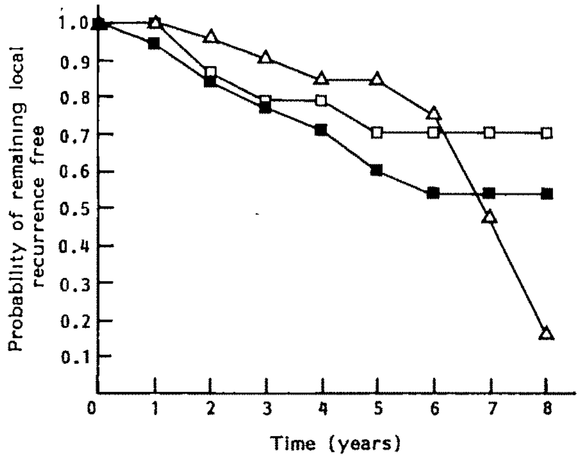
Number at risk									
□	184	170	119	89	69	34	24	11
■	57	46	31	20	14	7	5	2
△	22	19	14	11	6	4	4	3

Figure 3 *Nodal stage* versus *local recurrence.* □, *stage A=no nodal involvement;* ■, *stage B=low axillary node positive,* △, *stage C=internal mammary alone or both nodes positive,* $\chi^2=49{\cdot}0(2\ d.f.)$, $P<0{\cdot}001$, χ^2 *for trend*$=6{\cdot}43(1\ d.f.)$, $P<0{\cdot}02$ *(test for trend). The number of patients at risk during each time period is given*



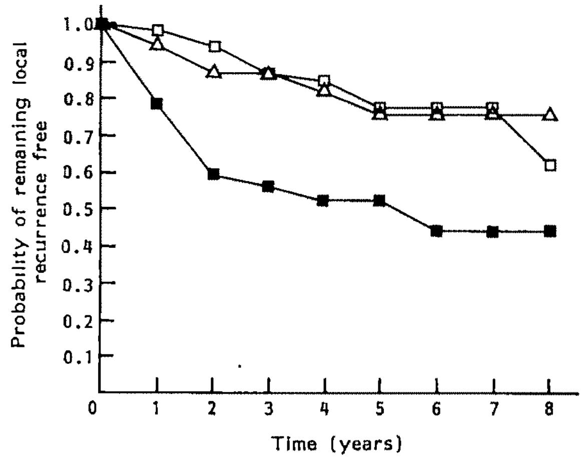
Number at risk									
□	51	49	36	29	22	12	7	4
■	212	184	128	93	68	35	27	13

Figure 4 *Grade* versus *local recurrence.* □, *grade 1,* ■, *grades 2+3,* $\chi^2=5{\cdot}58(1\ d.f)$, $P<0{\cdot}02$ *(patients with grade 1* versus *patients with grade 2 or 3). The number of patients at risk during each time period is given*



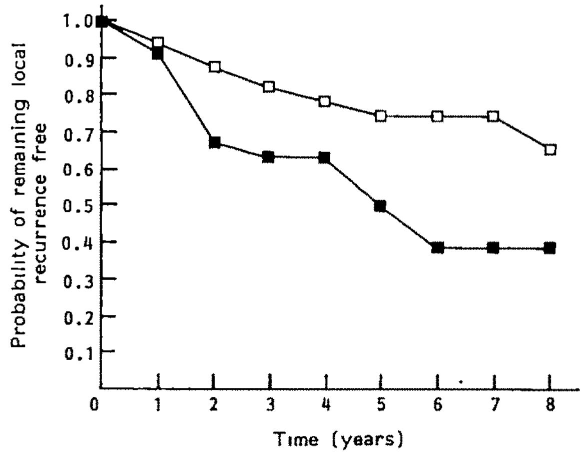
Number at risk								
□	60	57	38	27	23	12	10	4
△	25	25	20	16	14	9	7	2
■	55	49	37	29	24	11	7	4

Figure 5 *Completeness of excision* versus *local recurrence.* □, *complete excision;* ■, *incomplete excision,* △, *close excision;* χ^2*=1·78(2 d.f.), n.s.,* χ^2 *for trend=1·28(1 d.f.),* n.s. *The number of patients at risk during each time period is given*



Number at risk								
□	166	157	115	83	61	29	21	9
△	35	30	19	18	16	9	7	4
■	62	44	27	16	11	7	5	3

Figure 6 *Vascular invasion* versus *local recurrence:* □, *no vascular invasion,* ■, *vascular invasion present;* △, *vascular invasion suspected,* χ^2*=62·6(2 d.f.),* P<0·001; χ^2 *for trend=25·5(1 d.f.),* P<0·001. *The number of patients at risk during each time period is given*

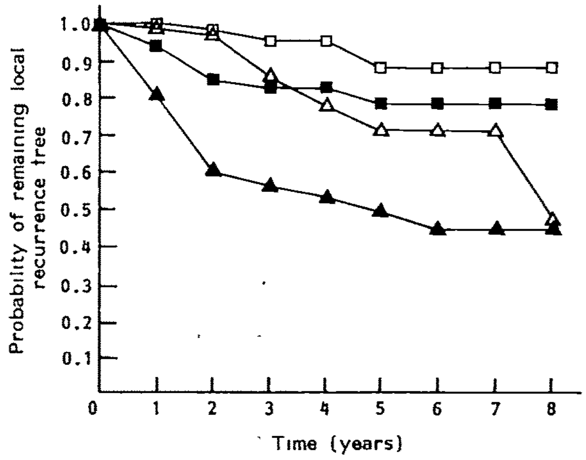


Number at risk								
□	230	202	144	102	77	39	31	16
■	33	30	17	15	11	6	2	0

Figure 7 *Quadrants ductal carcinoma* in situ versus *local recurrence:* □, *ductal carcinoma* in situ *in 0–3 quadrants,* ■, *ductal carcinoma in* situ *in 4 quadrants;* χ^2*=8·54(1 d.f.),* P<0·01. *The number of patients at risk during each time period is given*

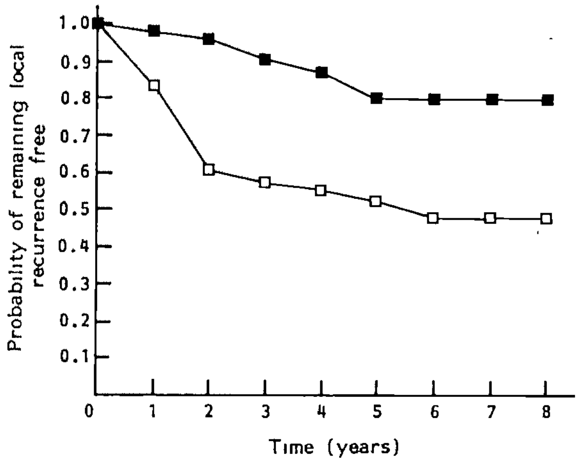
Table 3 *Cox's multivariate analysis*

Variable	*B* value	*z* value	*P* value
Vascular invasion	0·74	4·69	<0·001
Tumour size	0·247	3·22	0·003
Age	−0·059	−2·78	0·002
Lymph node stage	0·372	2·03	0·005



Number at risk								
□	66	63	39	28	18	7	3	0
△	66	63	48	33	28	16	13	5
■	66	58	41	34	26	11	8	5
▲	65	48	33	22	16	11	9	6

Figure 8 *Local recurrence* versus *prognostic index:* □, *quartile group 1,* ■, *quartile group 3;* △, *quartile group 2;* ▲, *quartile group 4,* χ^2*=34·5(3 d.f.),* P<0·001, χ^2 *for trend=25·6(1 d.f.),*P<0·001. *The number of patients at risk during each time period is given The ranges of index values calculted for each patient in the four quartile groups are 1= −2·5 to −1·04; 2= −1·0 to −0·51, 3= −0·5 to 0·33, 4= >0·34*



Number at risk								
□	88	67	42	30	22	14	11	6
■	175	165	118	86	65	30	21	9

Figure 9 *Local recurrence* versus *prognostic index:* □, *prognostic index ≥0;* ■, *prognostic index <0,* χ^2*=35·3(1 d.f.),* P<0·001. *The number of patients at risk during each time period is given*

in the two groups of patients with indices lying either side of 0 (*Figure 9*). In patients with high indices the risk of local recurrence by 5 years was 50 per cent compared with 20 per cent in patients with low indices.

Discussion

The rationale for breast conservation therapy is based on retrospective[5,6] and prospective[7–9] studies comparing this therapy with more radical treatment and showing no survival advantage for the latter. Increasingly, breast conservation is being offered to women with breast cancer. Opponents[10] argue that patients treated with less than mastectomy suffer unacceptably high recurrence rates within the treated breast. The published results, however, show great variation in local recurrence rates. Acceptably low rates of local recurrence have been reported by Bartelink and colleagues[11] (2 per cent at 6 years; 585 patients) and Sarrazin *et al.*[12] (5 per cent at 5 years; 592 patients). Higher rates have been shown by Bader and colleagues[13] (21 per cent at 5 years; 112 patients) and Harris *et al.*[14] (22 per cent at 15 years; 152 patients). Such varying results may have several explanations. Certainly patient selection is important and those studies, for example, that only included patients with small tumours (<2 cm) have the lowest recurrence rates. In addition, some studies do not include local recurrences occurring subsequent to or at the time of regional recurrence or distant relapse. This is apparent in some reports. Bartelink and colleagues[11] make the point that six patients were excluded from their analysis because they had clinical symptoms of distant metastases at the time of, or before discovery of, a local recurrence. Other reports may be less forthright. Our rate of local relapse appears high but does include all relapses irrespective of other regional or distant metastatic events. We have also included in our analysis breast relapses at a site different from the original tumour which could represent second primary tumours. In any event, these represent a failure of local treatment.

A major influence on local recurrence rate is the length of follow-up. Kurtz and colleagues[15] investigated the fate of 300 clinical stage 1 and 2 breast cancer patients treated with breast conservation. Ipsilateral breast recurrences continued to occur at 1 per cent per annum after the first decade of follow-up. Our patients have been followed for up to 8 years which is longer than several other series.

It appears that excision of a breast cancer without postoperative radiotherapy leads to a significantly higher rate of early local recurrence than after excision followed by radiotherapy[16]. The dosage may also be important and some institutions give higher doses than others. Although, as a result, the rate of local recurrence may be decreased, this may be to the detriment of good cosmesis. In our patients there were no poor cosmetic results and we certainly have not encountered the shrivelled fibrotic breast sometimes seen after radical radiotherapy, nor telangiectasia in the skin of the treated breast.

A number of studies have addressed which features may predict local relapse. Schnitt and co-workers[17] found that extensive intraductal carcinoma and high grade were important. Bartelink *et al.*[11] and Peterse *et al.*[18] reported an association between extensive ductal carcinoma *in situ* and subsequent local recurrence. One explanation for this is that ductal carcinoma *in situ* may be relatively radioresistant[19]; it is also frequently multifocal[20]. In our series we have confirmed that those patients with extensive adjacent ductal carcinoma *in situ* (4 quadrants) were more likely to suffer local recurrence than those with a less extensive component (0–3 quadrants; *Figure 7*).

In this study patient age, tumour size, histological grade, lymph node involvement, definitive vascular invasion and adjacent ductal carcinoma *in situ* all appear important. Completeness of excision does not appear to be predictive although data are not available on all patients.

We have shown an increased risk of local recurrence in the younger patients, confirming other reports[6,21]. This is clearly a problem as it is generally the younger patients who wish to conserve their breasts. The median age of patients in our study is 42 years and appears lower than in a number of other reports[12,22].

Other than patient age, three factors, i.e. tumour size, presence of vascular invasion and nodal stage, emerge from the Cox analysis as independent predictors of local recurrence. The prognostic index we have developed from the Cox analysis allows us to identify those patients who are at a high risk of local recurrence and who, in our opinion, should undergo mastectomy if unfavourable characteristics emerge from the histological examination of the excised tumour.

It has been claimed[15,23] that subsequent survival is not impaired in patients undergoing mastectomy for local relapse after conservation therapy compared with those suffering local recurrence after mastectomy as the initial treatment In addition, if local relapse can be controlled by subsequent mastectomy it need not present a major cause for concern. It is too soon to make these claims and data are required on the long-term outcome of patients who have undergone mastectomy for local recurrence after breast conservation. Furthermore it has been shown[24] that psychological morbidity is not reduced by breast conservation compared with mastectomy. A woman who suffers local recurrence is likely to suffer anxiety at a level comparable to that encountered when her tumour was first diagnosed There are, therefore, good reasons why attempts should be made to minimize local recurrence. Our main concern, however, is for those patients who have developed uncontrollable local disease; some have undergone extensive surgical resections, omental flaps and skin grafting but despite these measures the tumour has progressed relentlessly on the chest wall. Although 15 of the 18 patients with uncontrollable local recurrence had evidence of widespread disease and thus a dismal prognosis, we would wish to prevent these terminally ill patients having the additional stress of a large fungating tumour mass on the chest wall. In 13 (72 per cent) of these 18 patients with gross uncontrollable local disease the prognostic indices were greater than 0 and using our new criteria they would have been advised against breast conservation.

Many clinicians now advocate breast conserving surgery for primary breast cancer. The popular press has encouraged the belief that breast conservation is the treatment of choice and that mastectomy is an outdated and unnecessarily mutilating procedure. As a result many patients think that mastectomy is never indicated. We should exercise caution and not allow over-enthusiasm for what can be an excellent treatment option to cloud judgement, ultimately to the detriment of the patients. In practical terms our results would suggest that, in most cases, the presence of definite vascular invasion in a tumour should preclude breast conservation. We believe lymph node biopsy is important and will yield useful prognostic information which will help decide whether conversion to mastectomy or adjuvant therapy is indicated. The results of a recent study in 693 patients at this unit would suggest that we can omit the internal mammary node biopsy in patients who have laterally placed breast tumours; but in medial tumours biopsy of this node gives useful prognostic information. We have no intention of altering the dose of radiation given.

Had our index been available and applied to patients at the outset of this series the number eligible for breast-conserving surgery would have been reduced by 33 per cent using a cut-off of 0 (*Table 4*). Total local recurrences would have been reduced by 64 per cent and uncontrollable local recurrence by 72 per cent. A cut-off of +0·5 would not have allowed an adequate reduction in local recurrence and −0·5 would have excluded too many patients from the option of breast conservation

On the basis of our findings we have now altered our selection policy. Patient choice is a policy in our unit but those with tumours greater than 3 cm clinically or with

Table 4 *Predicted numbers of patients suitable for conservation and suffering local recurrence based on prognostic indices*

Index	Cases suitable for conservation	Local recurrence	Uncontrolled local recurrence
Not applied	263	56	18
Cut-off +0·5	213 (81)	33 (59)	9 (50)
Cut-off 0	176 (67)	20 (36)	5 (28)
Cut-off −0·5	134 (51)	16 (29)	3 (17)

Values in parentheses are percentages

mammographic evidence of extensive or multifocal disease are advised to undergo mastectomy. After operation, patients whose clinicopathological features put them at high risk of local recurrence would be advised to have mastectomy. We now intend to prospectively determine if such a change in policy will reduce the rate of local recurrence.

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Thyroid lymphoma

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We have reviewed the local experience of 15 cases of thyroid lymphoma with a view to documenting the epidemiology, presentation, management and prognostic factors governing outcome for this rare condition. All the patients were European despite the fact that 15 per cent of the local population is either Maori or Polynesian. The average age at presentation was 62 years and 13 of the 15 patients were women. The duration of symptoms was short: on average 9 months. Where feasible a definitive resection of the lesion was performed but this could only be performed in six of the 15 cases. The commonest histological type was non-Hodgkin's lymphoma which accounted for 14 of the 15 cases with the large cell variant being the most common (five cases). The mean period of follow-up was 3·3 years: only eight patients were alive and well at that time. The prognostic factors that influenced outcome were: (1) the histology of the lesion – large cell lymphoma carried a bad outlook; (2) whether the lesion could be totally resected or not – five out of six patients undergoing total resection remain alive and well; (3) the presence of pre-existing Hashimoto's thyroiditis was a favourable prognostic factor as only one patient without underlying Hashimoto's disease or positive antithyroid antibodies was alive at the end of the study; (4) male sex may also be an unfavourable prognostic factor as both men in the study died of disease 0·3 and 5 years after diagnosis.

Keywords: Thyroid, lymphoma, thyroiditis

Primary thyroid lymphoma is a rare condition accounting for approximately 2 per cent of lymphomas[1–3]. Controversy continues regarding the exact incidence of this condition as well as what prognostic factors govern outcome and what constitutes optimal management. Difficulties in histological differentiation of malignant lymphomas from small cell anaplastic carcinoma and background thyroiditis no doubt contribute to this[3,4].

Auckland is a good area to review the epidemiology of primary thyroid lymphoma as it has a European population of approximately one million as well as the largest Polynesian and Maori populations in the world. In addition the majority of patients in the area are treated in the Public Health System, thus making records readily available.

We have therefore reviewed the local experience of this condition with particular reference to: (a) the relative incidence in European, Maori and Polynesian populations; (b) the sex and age distribution of patients with this condition; (c) the common histological types of lymphoma presenting as a thyroid mass; (d) the effect of a variety of treatment modalities; (e) prognostic factors that influence outcome.

Patients and methods

A retrospective review was performed from the lymphoma files of the haematology, oncology, endocrinology and pathology departments of Auckland public hospital

Two patients with a previous diagnosis of 'small cell anaplastic carcinoma of the thyroid' had their histology reviewed using immunohistopathological staining. As a result, one patient was reclassified as thyroid lymphoma while the other retained the original diagnosis

Results

A total of 15 patients were found to have primary thyroid lymphoma from a total of 720 lymphoma files. The patients were seen in one of the Auckland Hospitals over the period 1976–88.

Histology was classified using the modified Rappaport classification (1979). Under this classification, 'large cell' lymphomas refer to non-Hodgkin's lymphomas of the diffuse, histiocytic type.

The epidemiology details, presentation, histology, management and outcome are summarized in *Table 1*. All patients had a chest X-ray, and other diagnostic investigations included thyroid scintiscan (nine of 15 patients), thyroid ultrasound (eight of 15), bone marrow aspirate and trephine biopsy (11 of 15), abdominal computed tomographic scan (six of 15) Thirteen patients were tested for thyroid antibodies and of these seven were positive.

Discussion

In general terms our findings help to answer some of the questions raised in the introduction. Firstly, regarding the racial and sex characteristics of thyroid lymphomas, there were no Maori or Polynesians with thyroid lymphoma despite 15 per cent of the population being Maori or Polynesian. The disorder is far more common in women, as previously noted[2,5,6], and both men who developed this disorder were dead of the disease at the time of review. The mean age of onset was 62 years with only two patients aged less than 50 years at presentation, and there was no obvious association between age of onset and outcome.

The single most common histological type was non-Hodgkin's lymphoma, 'large cell' type. This is consistent with other studies[2,3,6]. The next most common types were unclassifiable lymphoma and well differentiated lymphocytic. Non-Hodgkin's lymphoma of the large cell type was associated with a bad outlook: four of the five patients were dead of disease at the time of the study and the other had only been followed for 2 months. Other histological types had a variable prognosis.

Aggressive treatment with multimodality therapy did not appear to have a major impact on outcome. Of the patients who underwent some form of surgical resection coupled with radiotherapy and chemotherapy, three of four patients died. Only six patients had completely resectable tumours but of these five were alive and well with a mean follow-up of

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Table 1 *Patient details*

Patient No.	Race	Age (years)	Sex	Duration of symptoms (months)	Type of surgery	Histology	Stage	Treatment (radiotherapy, chemotherapy)	Follow-up (years)	Outcome	Pre-existing Hashimoto's
1	European	43	F	11	Biopsy	Non-Hodgkin's lymphoma, large cell	Located to neck but extra thyroid disease	36 Gy CHOP	0·7	Dead of disease	No
2	European	79	F	18	Biopsy	Non-Hodgkin's lymphoma, small cell	Located to neck but extra thyroid disease	36 Gy	14	Alive and well	Yes
3	European	55	F	5	Total thyroidectomy Neck dissection	Non-Hodgkin's lymphoma, well differentiated lymphocytic	Systemic disease	CHOP	1	Alive and well	Yes
4	European	55	F	36	Lobectomy Neck dissection	Non-Hodgkin's lymphoma, plasmacytoma	Located to thyroid and regional nodes	—	5	Alive and well	Yes
5	European	78	F	3	Biopsy	Non-Hodgkin's lymphoma, large cell	Systemic disease	36 Gy	0·3	Dead of disease	No
6	European	55	F	7	Biopsy	Non-Hodgkin's lymphoma, histiocytic-nodular	Located to neck but extra thyroid disease	36 Gy MATCOP	5	Alive and well	Yes
7	European	69	F	1	Total thyroidectomy Neck dissection	Non-Hodgkin's lymphoma, large cell	Located to thyroid and regional nodes	PEP CHOP	1	Dead of disease	Yes
8	European	68	M	5	Biopsy	Non-Hodgkin's lymphoma, no further classification	Located to neck but extra thyroid disease	34 Gy MATCOP	0·3	Dead of disease	No
9	European	51	F	36	Lobectomy	Hodgkin's	Located to neck but extra thyroid disease	40 Gy	8	Alive and well	No
10	European	87	M	2	Biopsy	Non-Hodgkin's lymphoma, large cell	Located to neck but extra thyroid disease	27 Gy PEP	5	Dead of disease	No
11	European	62	F	2	Biopsy	Non-Hodgkin's lymphoma, well differentiated lymphocytic	Located to neck but extra thyroid disease	44 Gy	0·3	Dead of disease	No
12	European	58	F	3	Biopsy	Non-Hodgkin's lymphoma, mixed	Located to neck but extra thyroid disease	36 Gy	4	Alive and well	No
13	European	37	F	2	Total thyroidectomy	Non-Hodgkin's lymphoma, large cell	Located to thyroid	36 Gy	0·2	Alive and well	Yes
14	European	60	F	2	Lobectomy	Non-Hodgkin's lymphoma, poorly differentiated lymphocytic	Located to thyroid	—	5	Alive and well	Yes
15	European	67	F	2	Biopsy	Non-Hodgkin's lymphoma, no further classification	Located to neck but extra thyroid disease	40 Gy	0·2	Dead of disease	Yes
Totals	European 15	(62)*	F 13	(9)*	Biopsy 9 Total thyroidectomy 3 Lobectomy 3 Neck dissection 3	Non-Hodgkin's lymphoma 14 Large cell 5 Well differentiated lymphcytic 2	Located to neck but extra thyroid disease 9 Located to thyroid and regional nodes 2 Located to thyroid 2 Systemic disease 2	Radiotherapy 11 Chemotherapy 6	(3·3)*	Dead of disease 7 Alive and well 8	8

* Values are means; CHOP, cyclophasphamide, Adriamycin, vincristine, prednisone; MATCOP, methotrexate, Adriamycin, teniposide, cyclophosphamide, vincristine, prenisone; PEP, prednisone, teniposide, cyclophosphamide

3–4 years. Indeed, two patients undergoing surgery were alive and well at 5 years. Eleven patients received radiotherapy and of these six were dead at the time of the study. Six patients were primarily treated with chemotherapy and of these four were dead. On this basis, it is hard to be sure about which therapeutic modality is most appropriate. The literature appears divided and although some authors suggest biopsy and radiotherapy is sufficient to treat all localized thyroid lymphomas[1,6], many authors note a survival advantage in patients with macroscopic removal of tumour along with radiotherapy[2,5,7]. Irradiating the anterior mediastinum as well as the neck has not clearly been shown to improve survival. For patients with mediastinal extension or systemic disease, combined surgery and radiotherapy appear to offer inferior results to using surgery with adjuvant chemotherapy[8].

Overall, after considering our own data and the data available in the literature, it appears that if total resection is possible the outcome is favourable, while biologically unfavourable tumours are little influenced by multimodality therapy. In addition, as mentioned above, the histological type 'large cell' carries a poor prognosis.

The association between thyroid lymphoma and Hashimoto's disease has been recognized for many years[9,10]. In our study eight patients had definite background Hashimoto's thyroiditis and ten had positive serology for thyroid antibodies. The presence of underlying Hashimoto's disease appeared a favourable prognosis indicator, as only one patient without underlying Hashimoto's disease or positive antibodies was alive at review.

There was no clear correlation between the stage of disease presentation and outcome. Both patients with disease localized to the thyroid gland were alive and well after 2–6 years follow-up but there was no difference in survival amongst patients presenting with localized extrathyroid disease, nodal or systemic disease. Some series have shown a poorer prognosis in patients presenting with nodal or systemic disease[11], while data from others support our findings[12].

We conclude:

1. Thyroid lymphoma is primarily a disease of older women
2. Most patients have a short history and have disease that is localized to the neck but unresectable due to invasion of adjacent vital structures
3. The commonest histological type is non-Hodgkin's lymphoma 'large cell' and this carries a poor prognosis
4. There is a strong association between thyroid lymphoma and Hashimoto's disease and the presence of underlying thyroiditis appears to be a favourable prognostic factor
5. Surgical excision should be performed where possible and in patients requiring adjuvant therapy for residual or recurrent disease the outcome is poor despite multimodality therapy.

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Wide local excision as the sole primary treatment in elderly patients with carcinoma of the breast

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Clinically localized carcinoma of the breast in 96 women was treated by wide local excision alone. The locoregional recurrence rate was 35 per cent at a mean follow-up of 47 months. There was no significant effect of recurrence on survival because of the relatively high mortality rate from unrelated conditions in these mainly elderly patients. Recurrence was successfully managed with tamoxifen in the majority of cases, with few patients requiring radiotherapy or further surgery. Recurrence in the breast was associated with significantly less systemic disease and mortality than recurrence in the axilla.

Keywords: Breast cancer, wide local excision

In recent years increasing interest has developed in conservative surgery for early breast cancer. In addition to an improved cosmetic result this form of treatment is associated with less operative morbidity and possibly fewer long-term psychological problems than more radical procedures. Several prospective studies have reported similar survival rates following radical mastectomy, total mastectomy, or partial mastectomy combined with postoperative irradiation[1–3]. Radiotherapy after conservative surgery for breast cancer reduces the local recurrence rate but has not been shown to improve overall survival[3,4]. Recurrence rates following conservative surgery without radiotherapy vary from 6 per cent[5] to 37 per cent[6]. Hermann[7] has recently reported similar locoregional recurrence rates (approximately 11 per cent) after partial, total and radical mastectomy in selected patients in an uncontrolled study. However, it is not clear how many of the patients in the partial mastectomy group underwent radiotherapy. Local recurrence in the breast after conservative surgery is more amenable to treatment and appears to be associated with a more favourable prognosis than recurrence after mastectomy which generally heralds systemic disease[4,7,8].

From the evidence available from many uncontrolled[4,5,9–13] and prospective, controlled[1–3] studies it would appear that a more conservative surgical approach to breast cancer is justifiable and that radiotherapy, which is not without complications[14,15], may be reserved for the treatment of the local recurrences that may result from such management. The aims of this study were first to quantify the local recurrence rate after wide local excision of breast tumours in a group of predominantly elderly women with clinically localized disease, and second to assess the management of locoregional recurrence after this form of treatment.

Patients and methods

Patients were offered wide local excision largely on the basis of advanced age or, in younger patients, where there was reluctance to undergo mastectomy. Evidence of systemic disease was excluded by physical examination, chest radiography and liver function tests. There were no specific limitations on tumour size for treatment by wide local excision nor was the presence of clinically enlarged mobile axillary nodes considered a contraindication to this treatment.

The surgical technique involved either a radial or circumferential incision usually including an elipse of skin over the tumour. The aim was to achieve macroscopic clearance of at least 1 cm of the tumour margins Tumours were bisected in the operating room to ensure adequate macroscopic clearance. Axillary node dissection was not performed even in the presence of palpable mobile axillary nodes The breast tissue was repaired with interrupted absorbable sutures and the skin closed with interrupted silk or subcuticular absorbable suture Drains were not routinely used and patients were generally discharged within 48 h Follow-up was according to a standard protocol which included review 2 weeks postoperatively, every 3 months for 2 years and every 6 months thereafter.

No patients in this study received adjuvant therapy and clinically detected recurrence was initially treated with hormonal therapy, radiotherapy or further surgery with chemotherapy reserved for the treatment of further progression.

Statistical analysis was by χ^2 and Fisher's exact tests.

Results

Between 1969 and 1984, 96 patients with a mean (s.e.m.) age at diagnosis of 76(0·8) years underwent wide local excision (*Table 1*). The tumours were present in the lateral breast in 70 per cent of cases while in 20 per cent they were medial and in 10 per cent central. The mean (s.e.m.) tumour size on clinical examination was 3·7(0·2) cm, with four patients presenting with tumours greater than 5 cm in diameter. Palpable, mobile axillary nodes were present in 13 patients (14 per cent) at presentation. Histological classification of tumours is given in *Table 2*; over 70 per cent were infiltrating ductal carcinoma.

At the time of analysis (January 1988), eight patients had been followed up incompletely. Of the remaining 88 patients,

Table 1 *Age at diagnosis of tumour*

Age (years)	No of patients
<59	5
60–69	9
70–79	56
80–89	26

Table 2 *Histological classification of tumours*

Tumour type	*n*
Infiltrating ductal	70
Adenocarcinoma	7
Carcinoma (not otherwise specified)	4
Mucinous adenocarcinoma	3
Infiltrating Paget's	3
Intraductal carcinoma	2
Lobular carcinoma	2
Mucin producing carcinoma	1
Medullary carcinoma	1
Not known	3

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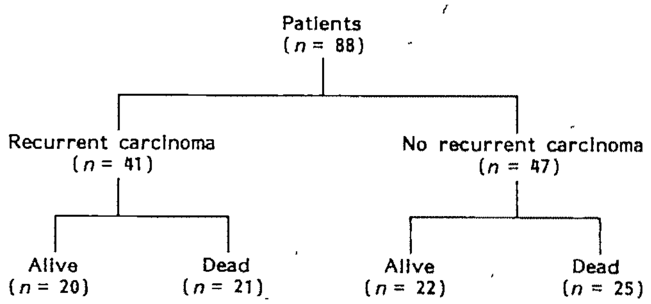

Figure 1 *Outcome in patients with breast cancer treated initially by wide local excision alone*

recurrent cancer had developed at a mean of 31 months in 41 patients (47 per cent), of whom 21 died (*Figure 1*). Of the 47 patients without clinical recurrent cancer, 25 died so that in this group of mainly elderly patients recurrence did not significantly affect survival ($P > 0{\cdot}05$, χ^2 test). Two patients died within 30 days of surgery (one mesenteric infarction and one myocardial infarction).

Locoregional recurrence occurred in 31 cases (35 per cent) at a mean of 31 months (range 3–120 months). Neither the presence of palpable nodes nor tumour size greater than 5 cm significantly increased the risk of locoregional recurrence ($P > 0{\cdot}05$, Fisher's exact test). In 15 patients (17 per cent) isolated ipsilateral breast recurrence occurred; 13 (15 per cent) developed isolated ipsilateral axillary recurrence and three presented with synchronous breast and axillary recurrence. In seven of the patients with axillary recurrence simultaneous systemic disease was present; this is significantly more than in patients with breast recurrence alone where only one patient had synchronous systemic disease ($P < 0{\cdot}01$, Fisher's exact test). The breast recurrences were related to the scar in 13 cases; only two appeared to develop elsewhere in the breast The relationship between tumour size and recurrence is shown in *Table 3*. The risk of breast recurrence tended to increase with increasing size, a trend that was not seen with systemic recurrence.

Tamoxifen was the initial treatment in 20 cases of locoregional recurrence. Tamoxifen proved significantly more effective in the treatment of isolated breast recurrence (response in ten of 11 patients) compared with isolated axillary recurrence (response in two of six patients, $P < 0{\cdot}03$, Fisher's exact test) when assessed by IUCC (International Union for Control of Cancer) criteria. One patient with isolated breast recurrence and two patients with combined breast and axillary recurrence failed to respond to tamoxifen and were subsequently controlled with further surgery[1] and radiotherapy[2].

In the remaining cases, control of locoregional disease was achieved with radiotherapy in eight and further surgical excision in one case. Two patients received no specific treatment for locoregional recurrence associated with advanced systemic disease.

Further progression after initial response was usually treated with radiotherapy, but in some cases further hormonal treatment (aminoglutethimide) or, rarely, chemotherapy was used. Four (22 per cent) of the patients with breast recurrence died of disseminated disease, significantly fewer than those with axillary recurrence, where nine (69 per cent) died of carcinomatosis ($P < 0{\cdot}03$, Fisher's exact test).

Only one patient in this study developed uncontrolled local recurrence. This patient developed axillary and supraclavicular node enlargement 20 months after the excision of a 2-cm infiltrating duct carcinoma. Initial treatment with tamoxifen achieved remission for 19 months after which the nodes reappeared. Radiotherapy again achieved local control for 9 months only to be followed by breast recurrence and further progression despite treatment with successive courses of hormonal (megestrol acetate) and finally chemotherapy. This patient died 6 years after wide local excision with extensive chest wall recurrence.

Discussion

The advanced age of the majority of patients in this study accounts for the high mortality rate in patients without clinical evidence of recurrence and prevents any conclusions on the effect of this form of treatment on survival. However, several large prospective studies have failed to show any survival benefit after radical surgery when compared with more conservative procedures with or without radiotherapy[1–3]. In previous studies, local recurrence has generally been managed by further surgery or radiotherapy. The introduction of tamoxifen has added a new treatment modality for breast cancer, and it is widely used in the treatment of advanced disease[16] and as an adjuvant in the management of early breast cancer[17]. Tamoxifen is also being used as the sole primary treatment in elderly patients. However, only approximately half the patients can be expected to respond, and a recent study comparing tamoxifen and excisional surgery in the management of elderly patients with breast cancer indicates a benefit in favour of surgery[18].

Of the 31 patients with locoregional recurrence, 20 were treated with tamoxifen initially and only seven of these progressed. Tamoxifen proved significantly more effective in the management of tumours recurring in the breast than in those recurring in the axilla. All but two of the remaining patients were treated with radiotherapy or surgery and did not require any subsequent treatment for locoregional recurrence. Only one patient developed uncontrolled local recurrence.

The locoregional recurrence rate of 35 per cent in this series of patients is considerably greater than that seen in studies where adjuvant radiotherapy is used but is similar to the rate seen in other studies where conservative surgery is the sole primary treatment (28 per cent, Fisher *et al.*[3], 37 per cent, Taggert[6]). Such recurrence rates have caused at least one study to be terminated in its early stages[6], despite the lack of convincing evidence that the increase in local recurrence reduces overall survival. The inclusion in the present study of large numbers of patients with T_2 (2–5 cm) tumours contrasts with the majority of previous reports in which only small tumours (< 2 cm) were treated by wide local excision but does not appear to have greatly increased the risk of locoregional recurrence. Furthermore, recurrence within the breast following conservative surgery appears to be more responsive to treatment and to have a more favourable prognosis than skin recurrence after mastectomy which is often associated with systemic disease and short survival[4]

It would appear that conservative surgery alone is an acceptable primary treatment particularly in elderly women who may find it difficult to comply with radiotherapy protocols. Careful follow-up is required to detect the substantial numbers of patients who will develop local recurrence. Local recurrence can usually be adequately managed with tamoxifen alone, enabling radiotherapy and further surgery to be reserved for those who fail to respond. By adopting this policy, more than 50 per cent of the patients in this study managed initially by wide local excision alone have avoided any treatment other than surgery. This approach may also be appropriate in the treatment of selected younger patients with breast cancer, particularly in view of the long-term adverse effects of radiotherapy on survival as demonstrated by Cuzick *et al.*[15] in an overview of radiotherapy trials.

Table 3 *Distribution of tumours by size and site of recurrence*

Tumour size (cm)	No of patients	Recurrence	
		Breast	Elsewhere
T_1 <2	33 (38)	6 (18)	10 (30)
T_2 2–5	51 (58)	11 (22)	12 (27)
T_3 >5	4 (4)	1 (25)	1 (25)

Values in parentheses are percentages

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Non-cyclical mastalgia: an improved classification and treatment

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A prospective study of 72 patients with non-cyclical breast pain was carried out. Non-cyclical breast pain was subdivided into true non-cyclical mastalgia (35 patients) and musculoskeletal pain (37 patients), the latter including Tietze's syndrome and other causes of chest wall pain. Mean age at presentation was significantly greater in the musculoskeletal group (39·3 versus *33·9 years) with a shorter mean duration of pain (14·7* versus *35·4 months) compared with the non-cyclical mastalgia group. True non-cyclical mastalgia was commonly bilateral and located within the upper outer quadrant of the breast, whereas musculoskeletal pain was almost always along the lateral chest wall or costochondral junctions and unilateral in 92 per cent of cases. Breast nodularity was present in 54 per cent of patients with non-cyclical mastalgia, but in only four cases (11 per cent) in the musculoskeletal group. Nine of 14 patients (64 per cent) with non-cyclical mastalgia obtained a good clinical response to drug therapy (over half responding to danazol alone); 19 underwent spontaneous remission, but there was a prolonged mean time to pain resolution of 27 months. In the musculoskeletal group 33 of 34 patients (97 per cent) had a good response to steroid and local anaesthetic injection; three resolved spontaneously without treatment, with a mean time to pain resolution of 17 months. This study indicates that differentiation of musculoskeletal pain from non-cyclical mastalgia may lead to more effective treatment with some prediction of the overall prognosis.*

Keywords: Non-cyclical mastalgia, classification, treatment

Mastalgia is the commonest breast symptom presenting to the general practitioner[1,2]. However, the relative reluctance of patients to seek medical advice[3] coupled with the antipathy towards mastalgia that has prevailed within the medical profession[4–6] has led to little scope for therapy. Some authors have continued to regard mastalgia as a trivial complaint with psychological origins about which they can do little, despite the fact that the widely held view that these women are neurotic has not been substantiated[7].

It was against this background of confusing terminology and ignorance of the aetiology of mastalgia that the Cardiff Mastalgia Clinic was established 15 years ago. The initial work enabled a classification to be developed based on clinical symptoms defining the different patterns of mastalgia[8] and its natural history[9]. Three discrete patterns of breast pain were defined: cyclical mastalgia, non-cyclical mastalgia and Tietze's syndrome. Classification of patients with mastalgia into homogeneous subgroups is obviously a prerequisite of any therapeutic study and subsequently enabled a series of randomized controlled trials to be carried out to assess new treatments of the various groups. There is strong evidence to support a hormonal aetiology in cyclical mastalgia[10,11], which responds well to endocrine manipulation[12,13]. Non-cyclical mastalgia, however, has a lesser response rate to hormonal therapy, and the small improvement over placebo response most probably reflects our lack of understanding of the aetiology of this disorder. This overall poor response may in part be due to inadequate differentiation of chest wall pain from true non-cyclical mastalgia, giving rise to inappropriate treatment in some cases.

When a specialist clinic is set up in a previously neglected field, there is an evolution of diagnostic criteria over the years, leading to an improvement in clinical classification of disease After exclusion of known causes of non-cyclical breast pain a larger group remains, which in our clinic was originally termed the 'periductal mastitis/duct ectasia' group[8]. A further study has led to another term, the 'trigger-spot zone' (along with a 'continuous pain' group) being proposed by Bishop and Blamey in Nottingham[14]. It is therefore clear that there remains a place for further improvement in the classification of non-cyclical mastalgia.

Over recent years in our clinic it has emerged that there is a discrete entity of localized lateral chest wall pain, as well as the medial Tietze's disease, which can be distinguished from non-cyclical breast pain itself by carefully recording the patient's history and by examination With the aim of improving the classification further, we carried out the present prospective study to see if improved differentiation of subgroups of non-cyclical breast pain leads to an improvement in management.

Patients and methods

Initial assessment

Patients with breast disease are first seen in the Cardiff Breast Clinic, which sees approximately 1200 new symptomatic patients per year Breast cancer is excluded by clinical examination, mammography and fine needle aspiration cytology, where indicated. Patients are then reassured of the benign nature of their condition and if the pain continues to be severe (and this is corroborated by a pain chart over 2 months) they are referred to the special mastalgia clinic.

The patients are then subdivided into three main subgroups of breast pain: cyclical mastalgia, non-cyclical mastalgia and musculoskeletal pain, the latter embracing Tietze's disease along with other causes of chest wall pain. Cyclical mastalgia refers to breast pain that occurs predominantly in the premenstruum and is relieved with the onset of a period. Non-cyclical mastalgia is experienced either continuously throughout the month or is intermittent with irregular exacerbations, but the pain and tenderness are always localized to the breast itself. The pain may be diffuse or localized, and when repeatedly localized to the same spot may be termed trigger-spot pain, although we have seen few of these patients.

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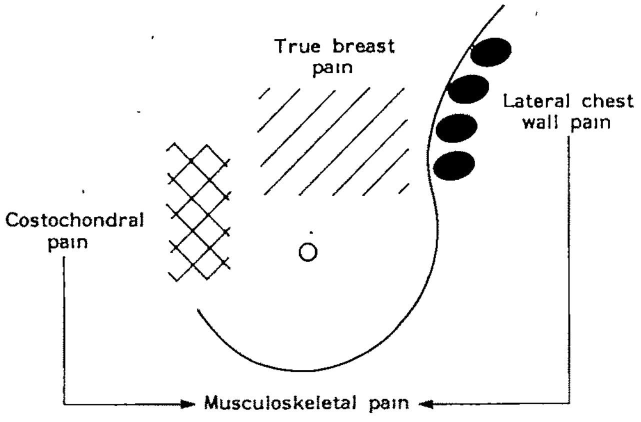

Figure 1 *Site of non-cyclical breast pain*

Chest wall pain may be discretely localized to the costochondral junctions (Tietze's disease) or may be sited more laterally in close apposition to the breast, leading to diagnostic confusion. In these cases careful examination technique will demonstrate that the pain originates from the lateral chest wall region (most commonly found just below the axilla, along the lateral border of the breast on the anterior axillary line), or indeed more medially, deep to the breast itself All these causes of chest wall pain have been grouped together as the musculoskeletal pain group in this study (*Figure 1*).

Examination technique is a crucial factor in the diagnosis of chest wall pain. Tenderness should be localized to a discrete area on the chest wall on examination, and palpation will often reproduce the pain. We have found it helpful to put the patient in the 90° lateral position, with the shoulder fully abducted and the ipsilateral hand behind the head, to aid full examination of the chest wall.

Patients

Over the 4-year period between May 1984 and April 1988, 72 consecutive patients with non-cyclical breast pain were studied prospectively. This group was further divided into 35 patients with non-cyclical mastalgia and 37 with musculoskeletal pain. Patients were regularly reviewed in the mastalgia clinic; initially this was every 1–2 months, increasing to a maximum interval of 3 months throughout the study.

Treatment

Patients with non-cyclical mastalgia were counselled on the various hormonal agents available to treat their condition and then, in accordance with the patient's wishes, offered a course of either danazol (eight), bromocriptine (four), evening primrose oil (six), medroxyprogesterone acetate (one), or simple withdrawal of the contraceptive pill (three); the remainder refused endocrine therapy As expected, multiple courses were required for several women to obtain a response, and those failing to achieve remission were offered analgesia or, as a last resort in one case, surgery.

Patients with musculoskeletal pain were all offered an injection of steroid with local anaesthetic to the exact site of the pain, but three patients declined treatment. This was given as a combined injection of 40 mg methylprednisolone in 1 ml of sterile aqueous suspension with 1 ml of 1 per cent lignocaine to the site at 6-weekly intervals, as necessary, up to a maximum of three injections, with a mean of 1·6 injections required per patient. The injection was always given to the precise spot where pain was localized during examination, usually close to the upper or lower borders of a rib (which also serves as a useful yardstick to assess appropriate depth of the injection) or at the costochondral junctions.

Statistics

The Student's t test was used to compare age at presentation, age at onset and duration of pain for both groups.

Results

Age at presentation

The histogram of the ages at presentation for the two groups of patients, those with true non-cyclical mastalgia and those with musculoskeletal pain, shows a significantly different distribution (*Figure 2*): a mean age of 33·9 years for non-cyclical mastalgia and a somewhat later presentation at 39·3 years for musculoskeletal pain ($P=0{\cdot}025$). The mean age at onset was also earlier with non-cyclical mastalgia (30·6 *versus* 38·4 years, $P=0{\cdot}0016$), but there was a similar range for both subgroups (16–61 years).

Menopausal status was similar in both groups, with the majority of women being premenopausal: 91 per cent of patients with non-cyclical mastalgia, 76 per cent with musculoskeletal pain.

Duration of pain

There was a significantly longer history of symptoms in the non-cyclical group with a mean duration of pain approaching 3 years compared with just over 1 year for musculoskeletal pain ($P=0{\cdot}0013$; *Table 1*).

Site of pain

Musculoskeletal pain was found to be unilateral in over 90 per cent of cases, whereas the non-cyclical group had a mixed spectrum with about half the patients experiencing bilateral pain (*Table 2*). Musculoskeletal pain was found to be along the lateral chest wall or localized to the costochondral junctions in 87 per cent of patients, the remainder being deep to the breast in the upper outer quadrant and other areas of the breast. In the non-cyclical group, however, the site of the pain was isolated to the upper outer quadrant in 80 per cent of patients with the remainder distributed throughout the other three quadrants.

Nature of pain

The character of the pain did not differ overall between the two groups and was usually described as an ache, or less commonly as a soreness, a drawing or a throbbing pain, which was of an intermittent nature in about half the cases in each group. However, radiation of the pain to the axilla or arm occurred in 60 per cent of patients with musculoskeletal pain,

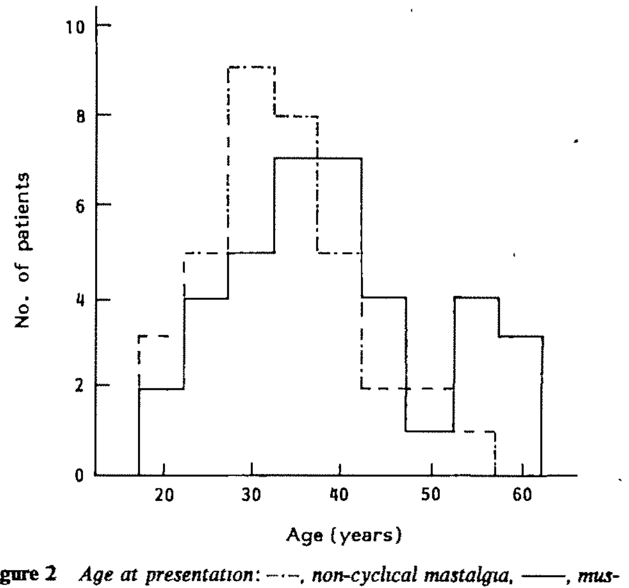

Figure 2 *Age at presentation*: —·—, *non-cyclical mastalgia*, ——, *musculoskeletal pain*

Table 1 *Duration of symptoms with non-cyclical breast pain*

	Duration of symptoms (months)	
	Non-cyclical mastalgia	Musculoskeletal pain
Mean	35·4	14·7
Range	5–156	2–48

Table 2 *Clinical features of non-cyclical breast pain*

Clinical feature	Non-cyclical mastalgia ($n=35$)	Musculoskeletal pain ($n=37$)
Site of pain		
Unilateral	17	34 (92)
Bilateral	18	3
Site of pain		
Chest wall	0	32 (86)
Breast		
Upper outer quadrant	28 (80)	2*
Remainder	7	3*
Radiation of pain to axilla/arm	17 (49)	22 (59)
Breast nodularity	19 (54)	4 (11)

Figures in parentheses are percentages. * Along the chest wall itself, beneath the breast

Table 3 *Events related to relief of non-cyclical breast pain*

	Non-cyclical mastalgia ($n=35$)	Musculoskeletal pain ($n=37$)
Treatment		
Drug therapy	9/14 (64)	*
Injection of steroid and local anaesthetic	*	33/34 (97)
Breast surgery	1	*
Simple analgesia	1	0
Other events		
Spontaneous remission	19	3
Menopause	0	0
Pregnancy	0	0
No remission	5	1

Figures in parentheses are percentages. * Treatment not given

compared with only 49 per cent of those with non-cyclical mastalgia. It was also interesting that breast nodularity was present in 54 per cent of patients with non-cyclical mastalgia, but in only 11 per cent of those with musculoskeletal pain, perhaps reflecting a hormonal factor in some of the non-cyclical mastalgia patients (*Table 2*).

Response to treatment

Nine of 14 patients with non-cyclical mastalgia given drug therapy (64 per cent) had a good clinical response, and over half responded to danazol alone (*Table 3*). In contrast, the vast majority (97 per cent) of patients with musculoskeletal pain responded to local steroid injection. Three patients with musculoskeletal pain refused therapy and subsequently obtained spontaneous relief, with a mean time to pain resolution of 17 months. Spontaneous remission was recorded in 19 of 21 patients with non-cyclical mastalgia who refused hormonal therapy, but the mean time to pain resolution was even more prolonged at 27 months. All therapies given achieved a response within 6 months of commencing treatment, emphasizing the need for improved early diagnosis and treatment of non-cyclical breast pain. Although these treatments were used exclusively in each group, the overall response to treatment was 97 per cent in the musculoskeletal group compared with 69 per cent in the non-cyclical mastalgia group. These two figures of clinical response are somewhat higher than those previously recorded in the overall treatment of non-cyclical breast pain in our clinic[12] and reflect the benefit of improved diagnostic differentiation and therefore specificity of treatment.

Prognosis

There was a higher relapse rate in the musculoskeletal group of around 33 per cent, with a mean time to first relapse of 9·2 months (range 2–32 months). The relapse rate in the non-cyclical mastalgia group was only 11 per cent for those treated successfully with hormonal agents but, as this was only a small group, this difference may prove to be spurious. However, although up to three local steroid injections may have been required, all but one patient in the musculoskeletal pain group achieved remission, whereas five patients (14 per cent) with non-cyclical mastalgia had not obtained remission of their pain at the time of assessment, with a mean follow-up of 9·9 months (*Table 4*).

Discussion

Many women are anxious that breast pain may indicate serious pathology, for example cancer, but the majority respond to simple reassurance when the discomfort is not severe. In a few patients with persistent mastalgia, the pain may be severe enough to interfere significantly with lifestyle, and these patients warrant treatment. Classification of these patients into homogeneous subgroups is an obvious prerequisite to any therapeutic study and this can be achieved in almost all cases referred to our mastalgia clinic.

Although most authors would agree on the criteria for differentiation of cyclical mastalgia and Tietze's disease[8], there does remain some controversy over the subdivision of the non-cyclical group. Bishop and Blamey have described 'trigger zone' and 'continuous breast pain' subgroups[14], which they treated empirically with simple analgesia or surgery (and local steroid injection in a few cases) with some success[15]. They also described two other small subgroups of spinal root syndrome and duct ectasia. It is well described that cervical radiculopathy may mimic breast pain[16], but as cervical spondylosis is not a true cause of breast pain it is better excluded (as indeed it is in our clinic) before a classification of non-cyclical breast pain is carried out The pathogenesis of duct ectasia is still unclear, but this condition may contribute to non-cyclical breast pain

Crile (who earlier referred to non-cyclical breast pain as 'fibrositis') has reported a good response to steroid injection of the breast itself for unilateral localized pain and tenderness[17]. He describes a similar mean age at presentation and response rate to our findings for musculoskeletal pain, which suggests that he may have been treating the same group of patients and achieved a response by virtue of the large volume of fluid injected (10 ml), which would produce a wide diffusion of steroid over the surrounding chest wall. It is interesting that the musculoskeletal pain group presented later with a shorter duration of pain, perhaps reflecting a greater propensity for muscular injury in this age group, although the exact aetiology of this disorder remains uncertain.

Most patients with mastalgia endure an undulating course of relapse and remission with the only prospect of relief being the advent of the menopause[9]. Spontaneous remissions do occur if treatment is not given but, as we have shown, there may be long intervening periods without relief of breast pain causing considerable reduction in the quality of life.

Non-cyclical mastalgia has a lesser response rate to hormone manipulation, compared with cyclical mastalgia, and several

Table 4 *Number of relapses for non-cyclical mastalgia and musculoskeletal pain after treatment or spontaneous remission*

No. of relapses	Non-cyclical mastalgia ($n=35$)	Musculoskeletal pain ($n=37$)
0	28	24
1	2	10
2	0	2
No remission	5	1
Mean follow-up time in months (range)	9·9 (2–30)	14·4 (3–46)

treatments may need to be tried before an optimum response is obtained. In this open study, however, we have shown that the clinical response of the non-cyclical mastalgia group to hormone therapy may be improved using this modified classification, thereby giving rise to a relative increase in the number of patients that may have a hormonal basis for their complaint. Further controlled studies are in progress to examine the efficacy of the injection therapy for musculoskeletal pain and hormonal therapies for non-cyclical mastalgia.

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Computer analysis in making preoperative decisions: a rational approach to lymph node dissection in gastric cancer patients

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In Japan, R_2 lymph node dissection is standard practice for all curatively resected gastric cancer patients. From 1969 to 1984, data were collected prospectively to evaluate this procedure and to provide information for a more rational approach to node dissection for each individual case. A total of 3843 cases was included in this study and an evaluation was made of the prognostic variables and lymph node involvement at various locations. Using a computer program, it is possible to compile a group of treated patients, with prognostic variables exactly matching those of an individual patient. Analysis of this group can then give an indication of the extent of lymph node dissection required for an individual patient. This paper gives a demonstration of the structure of such a system by means of an example.

Keywords: Computer analysis in diagnosis, preoperative diagnosis, lymph node distribution in gastric cancer, prognosis in gastric cancer

In future, computer analysis will become more and more accessible to physicians and specialists. For surgeons dealing with cancer, the treatment of an individual patient is based on preoperative assessment of prognostic variables, the extent of disease and knowledge of the outcome in earlier comparable cases derived from analysing large groups of patients. It would be valuable if morbidity and mortality data related to a specific individual patient were available.

In Japan, gastric cancer is the main cause of death The Japanese Research Society for Gastric Cancer (JRSGC)[1], advocated that a standard R2 resection should be the minimum procedure in the 1960s[2–5] based on several lymph flow studies (Reference 6 and K Ohta, M. Nishi, T. Nakajima *et al.*, personal communication) which demonstrated the anatomical pathways of metastasis. Although surgeons in Japan are convinced that gastric cancer should be treated primarily as a locoregional disease, the relationship between the primary tumour and the extent of lymph node dissection required remains unclear[7–11]. From 1969 to 1983, data were collected prospectively to evaluate the standard R_2 resection and facilitate rational decision-making regarding lymph node dissection in each individual. Lymph node involvement was evaluated for each location, as were prognostic variables, in 3843 cases entered in this study. In 1984 the computer program was introduced which made it possible to compile a group of treated patients, with prognostic variables exactly matching those of a specific individual patient Analysis of this group is now an important aid in deciding the extent of lymph node dissection required for the patient in question. This paper will show the structure of such a system, in practical terms, by means of an example.

Patients and methods

Data

Data from all patients who underwent resection for gastric cancer at the National Cancer Center, Tokyo, from 1969 up to and including 31 December 1983 were collected prospectively on an agreed protocol outlined by the JRSGC[1]. By the closure date, 3843 cases had been resected curatively or palliatively and were eligible for analysis. The success rate of the operations was evaluated according to the general rules of the JRSGC[1]

Double contrast X-rays were taken preoperatively to estimate the size of the primary tumour and extent of invasion Subsequently gastroscopy was performed and biopsies were taken for preoperative histological confirmation From 1984, endoscopic ultrasound was performed if the results were inconclusive Preoperative examination for the presence of metastases included rectal and gynaecological examination, chest X-rays, ultrasonography and, if required, computed tomography and bone scintigraphy. If patients had a solitary liver or peritoneal metastasis, curative resection was still considered possible[8] Patients with multiple or extensive metastases underwent palliative surgery and were excluded from the study

The seven preoperative variables considered to be important prognostic factors were registered, namely, sex, age, tumour type, depth of invasion, location, diameter of the primary tumour and histological type. Early (I, IIa, b or c, III)[1] and advanced (Borrmann I, II, III, IV)[13] gastric cancers could be classified accurately The following tumour location categories were used upper, middle or lower third of the stomach, and greater curvature, lesser curvature, anterior or posterior wall.

All patients underwent R_2 lymph node dissection, extending the dissection in some patients to N_3 and even N_4 nodes if necessary. In some cases a biopsy was taken from the para-aortic nodes (lymph node group No. 16). Immediately after the surgical procedure, the resected specimen was meticulously examined by the surgeon. All lymph nodes were dissected from the specimen and labelled according to the numbering system of the JRSGC (*Table 1*) Lymph nodes were examined histologically at three depths

Survival data were computerized every year after consulting the charts and the government registration statistics if data were missing There were no patients lost to follow-up Data were simply entered in an ASCII file database in a numbering system The program looks for specific numbering at certain locations within the ASCII string

Program

The program is written in MSDOS/Basic and was introduced in 1984 The program recalls and analyses, within only a few minutes, all cases that are similar to the patient in question. The computer identifies these patients by comparing the variables shown in *Figure 1* The first comparison is made on the basis of tumour location first, whether in the upper (C), middle (M) or lower (A) third and then whether in the lesser curvature (L), greater curvature (G), anterior wall (A) or posterior wall (P) The next branch choice is made according to the extent of invasion, then tumour classification, and finally the remaining variables are compared. When patients with the same variables are identified

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Table 1 *Lymph node location according to the numbering system of the Japanese Research Society for Gastric Cancer*

Number	Location
1	Right cardiac nodes
2	Left cardiac nodes
3	Nodes along lesser curvature
4	Nodes along greater curvature
5	Suprapyloric nodes
6	Subpyloric nodes
7	Nodes root left gastric artery
8	Nodes along common hepatic artery
9	Nodes at coeliac axis
10	Nodes at splenic hilus
11	Nodes along splenic artery
12	Nodes in the hepatoduodenal ligament
13	Retropancreatic nodes
14	Nodes at the mesenteric root
15	Nodes along the middle colic vein
16	Nodes along the abdominal aorta

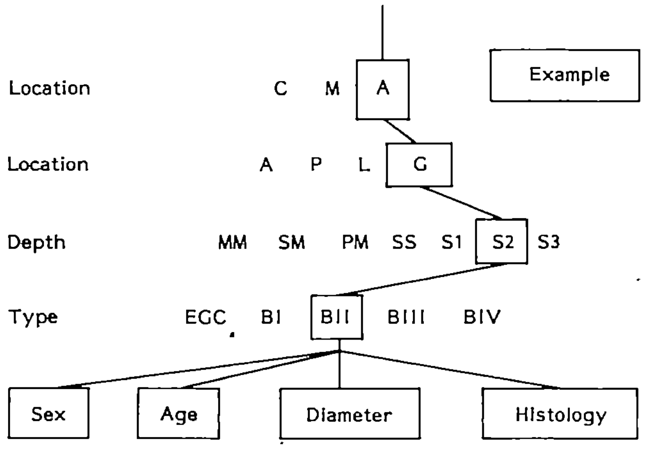

Figure 1 *Flow diagram of the computer program. Location (first line): C, upper third of stomach; M, middle third of stomach, A, lower third of stomach. Location (second line): A, anterior wall; P, posterior wall, L, lesser curvature, G, greater curvature. Depth MM, mucosa, SM, submucosa; PM, proper muscle layer; SS, subserosa; S1, into serosa, S2, through serosa, S3, into adjacent organs. EGC, early gastric cancer, B, Borrmann*

and collected, survival rate, cause of death and lymph node involvement can be analysed. The rate of lymph node involvement is defined as the proportion of positive locations of lymph nodes at any one site. Five-year survival rate was calculated according to the life table method. Patients who died were placed into the following categories according to the cause of death: local recurrence, peritoneal or liver dissemination, distant metastasis, other cancer, other disease and surgical mortality.

Results

In this study 3843 patients entered the database of whom 3265 were resected with curative intent. For the group having curative resection, in almost all cases (96·5 per cent) the preoperative diagnosis and classification correlated with the surgical findings. The extent of invasion could be accurately assessed because of the expertise of the radiologists[14]. The location of the primary lesion was used as first selection criterion to collect cases similar to the patient in question; 742 cases were available with tumour located in the upper third, 1651 cases with tumour located in the middle third and 1450 cases with tumour located in the lower third of the stomach (*Figure 2*). After this preliminary division the computer program ran through the previously mentioned variables to pick up equivalent values.

To illustrate this process a real example will be given. The patient was a 58-year-old man who complained of epigastric pain and weight loss. After preoperative examination he was thought to have advanced gastric cancer type BIII, probably with involvement of the serosa (S2). The primary lesion was located in the lesser curvature of the body of the stomach. The diameter was estimated to be 5 cm and the biopsy result read 'poorly differentiated adenocarcinoma'. After these data have been entered in the database, the computer analysis is displayed on the screen, as shown in *Table 2*.

Since the beginning of 1984, prospective evaluation of the system based on clinical experience in approximately 1000 primary gastric cancer patients has proved encouraging, although this evaluation was not done with a protocol.

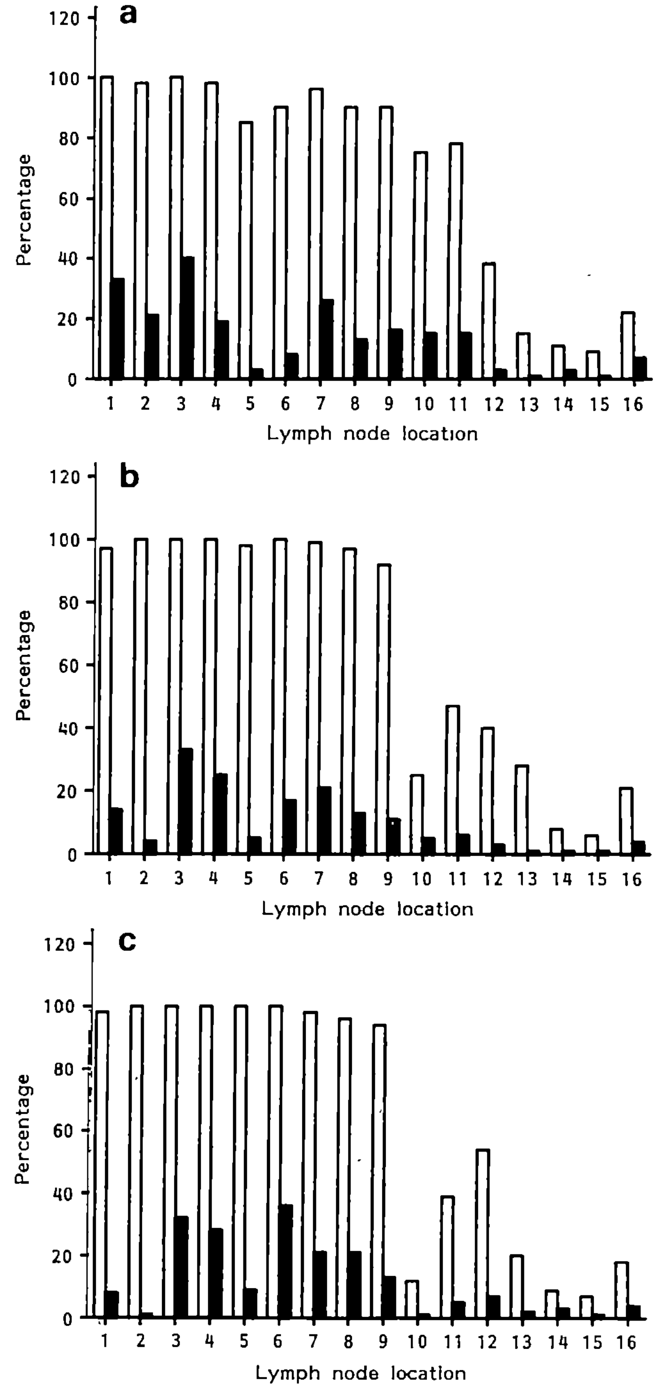

Figure 2 *Location of the primary lesion:* **a** *the upper third of the stomach (location C, n = 742),* **b** *the middle third of the stomach (location M, n = 1651),* **c** *the lower third of the stomach (location A, n = 1450).* ☐, *Histologically proved nodes,* ■, *metastatic rate*

Table 2 *Screen display after analysis*

```
PROGNOSIS AND LN-METASTASES OF THE PATIENTS WITH SAME FACTORS
            treated by gastrectomy in NCC, 1969–1983
PATIENT
        SEX and AGE          M  57 (+5/−5)
        TYPE and DEPTH       B3  S2
        LOCATION             A.      G.
        MAX DIAMETER         7·0 cm   (+2.5/−2 5)
        HISTOLOG TYPE        POR

DEPTH OF INVASION                    S1                    S2                    S3
TYPE OF CANCER                       B3                    B3                    B3
5 YEAR SURV RATE                     45·3%                 31·9%                 9 2%
GREENWOOD 5% ERR                     20 0%                 10·4%                 8 5%
NUMBER OF CASES                      28                    96                    61
LYMPH NODE METASTASIS meta/dissect (meta% in group)

       LN- 1                  4/27 ( 14·0%)        15/84 ( 16 0%)       10/39 ( 16 0%)
       LN- 2                  0/ 5 (  0·0%)         2/20 (  2·0%)        4/10 (  7 0%)
       LN- 3                 13/28 ( 46·0%)        65/88 ( 68 0%)       32/48 ( 52 0%)
       LN- 4                 14/28 ( 50·0%)        50/87 ( 52·0%)       33/48 ( 54·0%)
       LN- 5                  4/27 ( 14·0%)        15/87 ( 16 0%)       10/46 ( 16 0%)
       LN- 6                 15/27 ( 54 0%)        59/89 ( 61 0%)       37/48 ( 61 0%)
       LN- 7                 13/28 ( 46·0%)        42/85 ( 44·0%)       25/46 ( 41·0%)
       LN- 8                 10/28 ( 36 0%)        39/82 ( 41·0%)       29/44 ( 48 0%)
       LN- 9                  5/25 ( 18·0%)        20/81 ( 21 0%)       19/41 ( 31 0%)
       LN-10                  0/ 2 (  0·0%)         0/ 8 (  0 0%)        3/ 7 (  5 0%)
       LN-11                  2/ 7 (  7·0%)         8/40 (  8·0%)       14/22 ( 23 0%)
       LN-12                  2/10 (  7·0%)         9/56 (  9·0%)       11/27 ( 18 0%)
       LN-13                  1/ 4 (  4·0%)         2/22 (  2 0%)        6/10 ( 10 0%)
       LN-14                  0/ 1 (  0·0%)         1/ 8 (  1·0%)        7/ 9 ( 11 0%)
       LN-15                  1/ 2 (  4 0%)         1/ 5 (  1·0%)        1/ 3 (  2·0%)
       LN-16                  2/ 3 (  7 0%)         5/15 (  5 0%)        8/11 ( 13 0%)

[ CAUSE OF DEATH ]
LIVING NOW                   13 ( 46·0%)           32 ( 33·0%)          11 ( 18·0%)
UNKNOWN                       2 (  7·0%)            5 (  5·0%)           2 (  3 0%)
PERIT DISSEMI                 6 ( 21·0%)           23 ( 24 0%)          22 ( 36·0%)
HEPATIC META                  2 (  7·0%)            5 (  5 0%)           6 ( 10 0%)
LOCAL RECURR                  2 (  7 0%)           23 ( 24·0%)          11 ( 18 0%)
DISTANT META                  0 (  0 0%)            0 (  0 0%)           0 (  0·0%)
RECURRENCE                    2 (  7·0%)            5 (  5·0%)           7 ( 11 0%)
DIRECT DEATH                  0 (  0 0%)            0 (  0 0%)           0 (  0·0%)
OTHER CANCER                  0 (  0·0%)            1 (  1 0%)           0 (  0 0%)
OTHER DISEASE                 1 (  4·0%)            2 (  2·0%)           2 (  3 0%)

[ CURABILITY ]
ABS CURATIVE                 10 ( 36 0%)           27 ( 28 0%)           4 (  7·0%)
REL CURATIVE                 11 ( 39·0%)           37 ( 39·0%)           9 ( 15 0%)
REL NON-CURA                  2 (  7 0%)           13 ( 14·0%)           9 ( 15 0%)
ABS NON-CURA                  5 ( 18 0%)           19 ( 20 0%)          39 ( 64 0%)
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±, standard deviation, M, male; B, Borrmann; S2, through serosa; POR, poorly differentiated adenocarcinoma; A, lower third of stomach, G, greater curvature; META, actually involved node, DISSECT, dissected node; PERIT DISSEMI, peritoneal dissemination; ABS, absolute; REL, relative

Discussion

Data management and computer analysis have been used in all types of studies, retrospective as well as prospective in design. More and more hospitals are computerizing their administration and patient data. This paper emphasizes the value of continuously registering cancer patients' data for future studies. In our study of gastric cancer patients, the computer has proved to be an important tool in preoperative decision-making. As all relevant data and results are readily available it is possible to make a well-founded decision concerning the extent of lymph node dissection required for an individual patient.

The debate concerning the removal of lymph nodes is heated. It is widely accepted that incomplete removal of the tumour at resection increases the likelihood of locoregional recurrence. On the other hand, the effect of local recurrence on the survival rate of gastric cancer patients is still a matter of discussion in western literature. In Japan, however, it is accepted among surgeons that suspect lymph nodes at least should be removed. The JRSGC even advocates the standard dissection of lymph nodes one 'level' further than the one involved. The benefit gleaned from the removal of lymph nodes beyond metastatic nodes is debatable. In order to minimize postoperative morbidity, it is important to limit the extent of surgery to what is still oncologically acceptable.

Several lymph flow studies have shown certain pathways and a suggested layering of lymph node groups according to the distance from the tumour[6,15]. More recent studies, on the other hand, have revealed that the route of metastasis is not fixed (Reference 16 and K. Ohta *et al.*, personal communication). N_2 and even N_3 nodes can be skipped to allow metastasis directly to para-aortic lymph nodes. In our series the macroscopic classification of lymph nodes differed from the histological classification in 38 per cent of the cases. Gall and Hermanek have also observed a higher rate of lymph node metastases than expected preoperatively, by using a more extensive dissection[17]. In patients operated on curatively, 10–25 per cent of the lymph node groups 7–12 were involved. These lymph nodes would not have been resected by conventional gastrectomy, and are therefore impossible to classify accordingly.

Ordinary decision-making is based on 'average experience' derived from large groups[18]. However, with the computer program described we can individualize the problem by differentiating between important prognostic variables for any one particular case. Outcome is assessed from a prospectively collected database and represents the clinical facts on metastases at specific lymph node locations. For every node location the percentage of metastases is given. It is postulated that at least removal of suspect nodes is necessary to improve survival results. We therefore feel confident in using our analysis to justify to what extent lymph node dissection should be performed. Standard procedures can be abandoned as we know, within statistical limits, which nodes will be involved in a specific individual case. This has already led to a less aggressive approach, concerning pancreaticosplenectomy in general and for individual lymph node locations more specifically.

In conclusion we would like to emphasize the indispensible value of computer programs and instant analysis in preoperative decision-making for surgeons dealing with cancer. It is essential for workers in each cancer field to agree on a uniform system of data management, based on uniform staging policies. We hope that this example will encourage efforts to standardize data management in surgical oncology.

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Total gastrectomy and oesophagojejunostomy with linear stapling devices

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When performing total gastrectomy and oesophagojejunostomy with a circular stapling device two disadvantages are obvious; firstly, a purse-string suture is needed, and secondly the instrument can be extremely difficult to introduce if the oesophagus is narrow, so that the risk of rupture is substantial. We therefore developed the following technique. When the specimen is attached only to the oesophagus, and the Roux-en-Y loop has already been divided with a linear stapling device, a small incision is made on the back wall of the oesophagus and antimesenterically 6 cm distal to the cut end of the Roux-en-Y loop. The two forks of the GIA® or the PLC 50® instrument are introduced into the oesophagus and jejunum, and the two organs are brought together at the hiatus. The instrument is closed and fired. The residual opening is closed with a linear stapler which also includes the front wall of the oesophagus. With a knife, the oesophagus and excessive amounts of tissue are trimmed away, and the oesophagojejunostomy is completed. Fifteen patients (median age 67 years) had a postoperative hospital stay of 10 days (range 8–45 days) after this operation. Leakage occurred in one patient and one patient died. The anastomosis took 12 min to perform (range 8–20 min). Three reoperations were needed: intestinal obstruction, leakage and a negative exploration. The median width of the oesophagojejunal anastomosis 6 months after operation was 32 mm (range 27–40 mm). Oesophagojejunostomy performed with two linear staplers allows a quick and reliable anastomosis independent of oesophageal lumen size and a time-consuming purse-string suture.

Keywords: Total gastrectomy, oesophageal anastomosis, stapling device

The main reason for postoperative mortality after total gastrectomy is still anastomotic leakage[1,2]. After the introduction of circular stapling devices the time to perform the oesophagojejunal anastomosis has been reduced, which is a substantial benefit in such time-consuming operations[3]. Recently it has been shown in a prospective study that the outcome for patients undergoing total gastrectomy was better after a stapled (EEA® stapler, US Surgical Corporation and Auto Suture UK, Norwalk, Connecticut, USA, or ILS®, Ethicon Ltd., Somerville, New Jersey, USA) oesophagojejunostomy than after a hand-sewn anastomosis[4]. There are, however, at least two disadvantages with circular stapling devices in constructing oesophagojejunal anastomoses. Firstly, a time-consuming purse-string suture is needed and, secondly, the insertion of the instrument into a narrow oesophagus can be extremely difficult and oesophageal rupture is described[3]. In an attempt to eliminate these drawbacks we have developed a new technique, using two linear stapling devices for the oesophagojejunal anastomosis, which is independent of a purse-string suture or other stay sutures and of oesophageal width. This article describes the surgical procedure in 15 consecutive patients undergoing total gastrectomy and chosen at random to have the new technique. The width of the oesophagojejunal anastomosis was measured after 6 months using a fibreoptic endoscope and a balloon, and the results were compared with those of patients operated on with a conventional end-to-side oesophagojejunostomy performed with a circular stapling device[3].

Patients and methods

From May 1986 to April 1988, eight men (median age 68 years, range 41–81 years) and seven women (median age 67 years, range 38–74 years) underwent total gastrectomy because of cancer (12), lymphoma (two) or gastrinoma (one). Five of the 12 cancer patients had previously had a Billroth II resection because of benign disease; six had their tumour confined to the body of the stomach and one to the cardiac region. Six patients had tumour growth penetrating the stomach, and lymph node metastases were present in five. The patient with carcinoma of the cardia had a liver metastasis.

Operative procedure

Total gastrectomy, with omentectomy, splenectomy, and dissection of the lymph nodes around the coeliac axis and hepatoduodenal ligament was performed in all patients. An extended procedure was performed in seven patients, including resection of the pancreatic tail in five, enucleation of a gastrinoma in the pancreatic head in one and a small bowel resection in another one. Of the 15 operations, 13 were performed using a laparotomy alone, and the remaining two were conducted through a left thoracoabdominal incision. All patients were given prophylactic antibiotics (400 mg intravenous doxycycline hydrochloride, Vibramycin®, Pfizer Ltd., Sandwich, UK). Dextran 70 (Macrodex®, Pharmacia, Uppsala, Sweden) was used as the antithrombotic drug.

At the end of the *en bloc* resection the specimen was attached only to the oesophagus and was brought up to the patient's chest (*Figure 1a*). A Roux-en-Y loop of 50 cm length was prepared and divided with a linear stapling device. A small incision was made on the back wall of the oesophagus, using the stomach for traction, and antimesenterically 6 cm distal to the closed end of the Roux-en-Y loop (*Figure 1b*). The two forks of the GIA® (US Surgical Corporation and Auto Suture UK) or the PLC 50® (Ethicon Ltd.) instrument were introduced into the oesophagus and the jejunum respectively, and the two organs were brought together at the hiatus (*Figure 1c*). The instrument was closed and fired (*Figure 1d*). After withdrawing the instrument the remaining opening was closed with a linear stapler, which also included the front wall of the oesophagus (*Figure 1e*). With a knife the oesophagus and excessive amounts of tissue were trimmed, and oesophagojejunostomy

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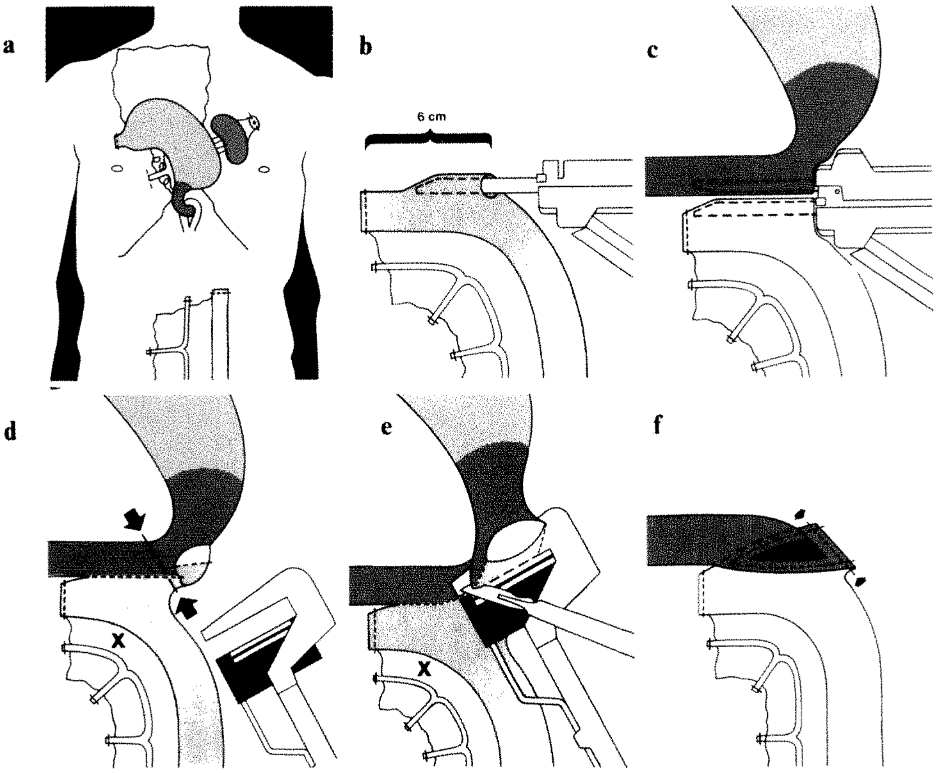

Figure 1a–f *End-to-side oesophagojejunal anastomosis after total gastrectomy with the PLC 50® or the GIA® and the RL 60® or the TA 55® stapling instruments. To avoid stapling the mesenteric border marked X* (**d, e**) *to the oesophagus, it is wise to insert the nasogastric tube before closing the residual opening*

was completed (*Figure 1f*). To accomplish the anastomosis in the left chest the specimen was brought up into the thorax through the hiatus and the anastomosis was completed in the same way as in the abdomen. When the opening after the GIA or the PLC 50 forks was closed with the TA 55® (US Surgical Corporation and Auto Suture UK) or RL 60® (Ethicon Ltd.) care was taken not to grasp the jejunal mucosa at the mesenteric border by pulling up too much of the jejunal lip (*Figure 1e*). On the other hand, it is important that the linear stapler encloses the staple lines of the GIA or PLC 50 instrument. This was facilitated by putting two Allis clamps one in each corner and 2–3 mm along the staple lines. With a slight lateral traction on the two clamps this manoeuvre also simplified closure of the opening by flattening it out. When a small piece of jejunum was seen on the specimen bridged to the oesophagus by cut staples and comprising a lumen, the anastomosis was considered to be intact. With the anastomosis under saline, integrity was checked by air inflation through the nasogastric tube. If a leak was present it was oversewn with an absorbable 4–0 suture. Otherwise no form of reinforcing stitches was used.

The time to perform the anastomosis (that is, the time from making the incisions in the oesophagus and jejunum to the closure of the oesophagojejunal opening with a linear stapling device (including the time to locate and oversew a leak) was measured by the anaesthetist. Frozen section examination of the resected margins was performed intraoperatively to ensure tumour clearance.

Postoperative regimen

The nasogastric tube was left with its tip well below the anastomosis, and the patient was fed intravenously for 5 days, after which the anastomosis was checked for leakage by X-ray films with water-soluble contrast medium. If no leakage was observed, the patient started to drink fluids, followed by a soft diet. On the seventh day, a regular diet was served and intravenous therapy was discontinued.

Follow-up

Six months after surgery nine patients were examined by endoscopy. The width of the anastomosis was calculated by inserting a Fogarty aortic occlusion catheter (American Edwards Laboratories, Irvine, California, USA) along with the endoscope. With a syringe connected to the catheter, air was inflated until the balloon in the distal end filled the anastomotic lumen. The balloon was pulled up and down a couple of centimetres to make sure that it was not getting caught but slid smoothly and just filled the anastomotic lumen. The volume inflated was noted on the syringe. This was repeated three times and the mean calculated. The air was exsufflated by pulling the piston of the syringe back but not disconnecting the syringe and the balloon catheter. After withdrawal of the endoscope and the balloon catheter, the latter was filled to the volume determined and the diameter of the balloon was measured with a caliper. This method of measuring the oesophagojejunostomy has been in use since 1984 in our department in a prospective series of patients having total gastrectomy and oesophagojejunostomy end-to-side with the EEA stapler. These patients served as controls when assessing the anastomotic width.

Statistical methods

The Kruskal–Wallis one-way analysis of variance by ranks was applied to test the difference between the three groups of stapled anastomoses. When a significant difference was noted, the Mann–Whitney *U* test was used to determine between which groups the difference was valid. When comparing two groups the Mann–Whitney *U* test was used directly.

Results

In all patients in whom we tried to perform the oesophagojejunostomy with the two linear stapling devices, we succeeded. To bring the oesophagus and jejunum together we used the GIA in 11 of the 15 patients and the PLC 50 in the remaining four. The residual opening was closed with the TA 55, staple height 3·5 mm (blue magazine), in nine patients and in six we used the RL 60, adjusted to the same staple height. The median operating time was 5 h 9 min (range 205–505 min) and the median time to perform the oesophagojejunal anastomosis was 12 min (range 8–20 min).

The postoperative complications are shown in *Table 1*. The patient who developed a leaking anastomosis was found to have no leakage on routine check of the anastomosis on the fifth postoperative day, but sudden onset of abdominal pain the day after made us explore the patient. The leakage was found in the corner between the two crossing staple lines. It was oversewn and drained and healed uneventfully within 2 weeks. The patient was discharged in good health after 28 days.

Table 1 *Postoperative complications and reoperations in 15 patients having total gastrectomy and oesophagojejunostomy*

	No.	Reoperations
Anastomotic leakage	1	1
Small bowel obstruction	1	1
Empyema	1	0
Lung embolus	1	1*

* This patient had a negative exploration and later died of a pulmonary embolus (hospital mortality one in 15)

The median postoperative hospital stay was 10 days (range 8–45 days). Extension of the operation by resection of the pancreas (six patients) increased the hospital stay to 13 days (range 8–36 days: Mann–Whitney $W=55$, $P=0{\cdot}44$, n.s.). Nine patients are alive 1·4–23 months after the operation.

At endoscopic examination 6 months after the operation the diameter of the oesophagojejunal anastomosis performed with two linear stapling devices was equal or superior to the EEA-stapled anastomoses (*Figure 2*). No patient complained of dysphagia.

Discussion

Oesophageal anastomoses with circular stapling devices must be considered safe when two large series report a leakage rate of 3·5 per cent[5,6]. There are, however, two main drawbacks: the need for a time-consuming purse-string suture and, in some cases, a narrow oesophagus; this can lead to a difficult and sometimes dangerous introduction of the instrument, which can result in oesophageal rupture[3]. Consequently many ingenious attempts have been made to facilitate the insertion of the anvil into the oesophagus. Alexander-Williams has proposed the use of a Mousseau–Barbin tube trimmed to cover the anvil; pulling the tube allows the anvil to be gently introduced into the oesophagus[7]. Chung *et al.* favoured dilatation of the distal oesophagus with a balloon catheter before insertion of the instrument[8]. However, none of these methods excludes the use of the purse-string suture. With this in mind we have been looking for a method that eliminates the need for a purse-string suture and the need for stay sutures or clamps in the oesophagus during the anastomotic procedure. We found the present method to be of great value in these respects because the size of the oesophagus is completely irrelevant.

It can be argued that in cases where there is a narrow oesophagus the oesophagojejunal anastomosis can be manually performed. There are, however, two arguments against this contention: time and standardization. The stapled anastomosis is quicker to perform than the hand-made anastomosis, both experimentally and clinically in randomized series, and reduction in overall operation time is relevant to the lower incidence of thromboembolic complications seen in stapled series[9,10]. Secondly, stapling instruments are unsurpassed for standardization, which is known to be an important factor for quality.

The time to perform the oesophagojejunal anastomosis with two linear staplers compares well with other staple methods, for instance oesophagojejunostomy end-to-side with a circular stapling device (12 and 20 min, respectively)[3]. The type and rate of complications seen in the present series are expected in this kind of surgery. What the leakage frequency will be in the long run cannot be predicted from this pilot series but our experience seems to correspond to that of others[1,2,11].

West *et al.* found stricture frequency to be inversely correlated to the size of the stapler in a series of patients having oesophageal resection and oesophagogastrostomy[12]. The true incidence of strictures in oesophageal anastomoses can be determined only by endoscoping all patients postoperatively, and Wong *et al.* have shown that most strictures are seen within 6 months[6]. It is well known that a narrow anastomosis can escape detection because of absence of dysphagia and conversely that the patient can complain of difficulty in swallowing with a wide anastomosis. The width of the oesophagojejunal anastomoses in the present series compares well with the circularly stapled anastomoses, particularly when one considers that patients operated on with linear staplers often include those with a very narrow oesophagus.

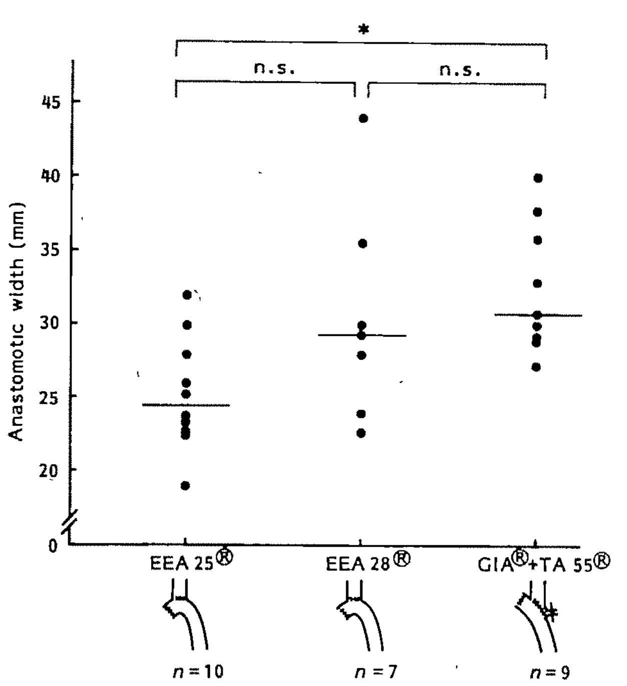

Figure 2 *The anastomotic diameter after 6 months in patients having total gastrectomy and different types of stapled oesophagojejunostomy Of the 15 patients operated on with the new method (GIA® + TA 55®) six patients were not investigated at 6 months postoperatively because three patients were dead or dying at that time, two refused investigation and one had not yet qualified Test for differences (see* Statistical methods) *EEA 28* versus *EEA 25 and GIA+TA 55, no significant difference; * EEA 25* versus *GIA+TA 55,* $P<0{\cdot}05$; ——, *median*

The anastomosis is partly inverted and partly everted with two corners of intersecting staple lines (*Figure 1f*) and hence there is a risk for ischaemia in that area. A large clinical experience attests, however, to the safety of intersecting staple lines both in intestinal and lung surgery, presumably owing to the fact that the blood flow continues through the intersecting staple lines[13]. None the less, the only leak in the present series arose in the corner of intersecting staple lines. Whether this was due to ischaemia or to technical failure could not be determined at relaparotomy. At the primary operation, 5 days earlier, however, the anastomosis was airtight under a pool of saline.

When the operation had to be extended to the left chest the anastomosis was easily completed in the same way as in the abdomen. However, we have no experience in performing a high oesophagojejunal anastomosis in the right chest with this technique. The curve always at hand at the end of a long jejunal loop fits better with the old end-to-side anastomosis where the circular stapler is introduced through the open jejunal end to the oesophagus[3].

Extension of the operation by resecting the pancreatic tail did not influence the postoperative hospital stay. This confirms the experience of Sadek *et al.*[14], but is in contrast to that of others[15]. As most surgery for gastric carcinoma is palliative, postoperative morbidity and mortality rates should be low and the hospital stay short. Dysphagia should be absent for the rest of the patient's life. We consider that oesophagojejunostomy performed with two linear staplers fulfils these demands in the present pilot study.

Acknowledgements

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Short note

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NdYAG laser treatment in the palliation of advanced oesophageal malignancy

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Carcinoma of the oesophagus is a common disease responsible for 3700 deaths per year in the UK[1]. Dysphagia is often the first symptom, by which time 50 per cent of patients are beyond the reach of curative surgery[2]. The results of surgery are poor although surgery has often been considered the best palliation[3]. The neodymium yttrium aluminium garnet (NdYAG) laser has considerably advanced the management of this condition and is suggested to be associated with lower mortality and morbidity rates than various forms of stenting tubes[4]. This paper describes the results with our first 51 patients.

Patients and methods

Fifty-one patients with malignant strictures of the oesophagus were investigated. The male:female ratio was 1·7·1 and the median age was 76 years (range 49–92 years). Seventy-five per cent of patients were older than 70 years. All patients had positive histology before treatment: 43 had adenocarcinomas and eight had squamous carcinoma. The strictures commenced between 18 and 40 cm with a median length of 5 cm (range 2–14 cm). The adenocarcinomas commenced between 28 and 40 cm and the squamous tumours proximal to 30 cm. All patients were considered inoperable because of age, concomitant disease, generalized metastases or advanced local disease on computed tomograpic scan Swallowing was assessed by an independent observer before and after treatment. The 'dysphagia index' was assessed according to ability to swallow: 0, all solids, 1, most solids, 2, semisolids; 3, fluids, 4, nothing[6]. All procedures were performed under intravenous sedation with diazepam using the Olympus GIF 2T10 (Olympus Ltd., Tokyo) twin suction channel endoscope. A NdYAG laser of wavelength 1064 nm was used. A non-contact method was employed where possible with a power of 70 W for 1 s and a total energy dosage between 5000 and 10 000 J per treatment An average of two sessions separated by 72 h was required to open a satisfactory lumen. Treatment was repeated after 1 month and the rate of tumour progression was assessed at that stage. Follow-up treatments were performed at intervals of 3–12 weeks dependent upon progression of tumour and recurrence of symptoms.

Results

In all 166 treatments were given, an average of 3·3 per patient. On 34 occasions wire-guided dilatation with Celestin® (Medoc, Gloucester, UK) bougies was necessary. On 17 occasions a guidewire would not pass and the direct contact sapphire-tipped laser endoprobe using a power of 15 W was required to create a lumen.

The dysphagia indices before and after treatment are shown in *Figure 1*. Three patients failed to complete the first course of treatment:, two died of aspiration pneumonia and one was perforated at dilatation. In 44 of the remaining 48 cases swallowing was improved. This improvement in median dysphagia index from 3 to 1 is significant ($P<0\cdot0001$, Mann–Whitney U test). The long-term results in patients surviving more than 2 months are shown in *Figure 2*. Swallowing was significantly improved over pretreatment values at 2, 4 and 6 months ($P<0\cdot0002$). Of the 51 patients, 24 died in the first 2 months, and six and three died before 4 and 6 months respectively. Of the six patients surviving longer than 6 months, five have now died within 6–9 months of their first treatment with dysphagia indices of 0–2, and one is still alive with a dysphagia index of 1 after 6·5 months. Three patients, after surviving for 2, 2 and 6 months respectively, developed rapid progression of symptoms owing to circumferential tumour stenosis with extrinsic compression. Laser therapy produced only transient relief of symptoms and endoscopic intubation with an Atkinson® tube (Key Med, Southend-on-Sea, UK) was necessary. With the exception of two individuals who were lost to follow-up the remaining eight patients are alive and under review at a median time of 3 weeks (range 1–12 weeks) after their first treatment.

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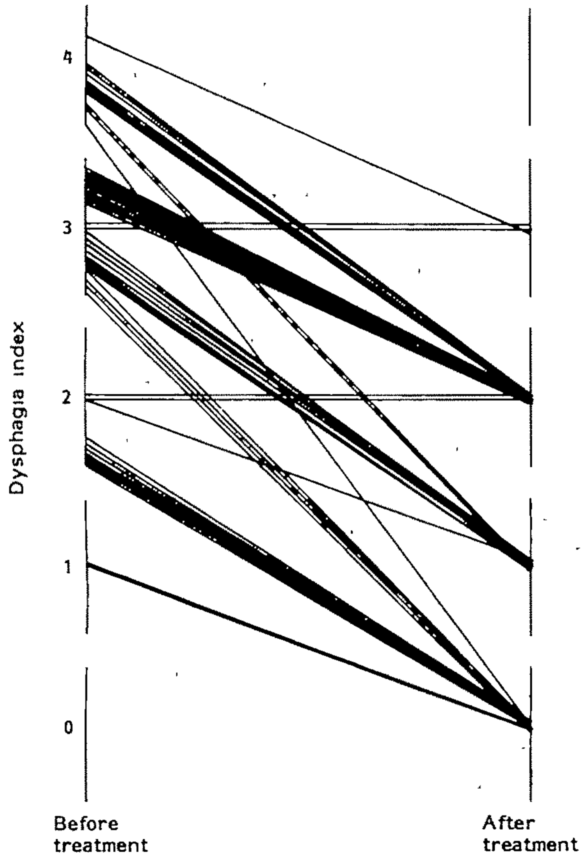

Figure 1 *Swallowing indices before and after the first course of laser treatment. Dysphagia index assessed as ability to swallow 0, all foods, 1, most solids; 2, semisolids; 3, fluids, 4, total dysphagia*

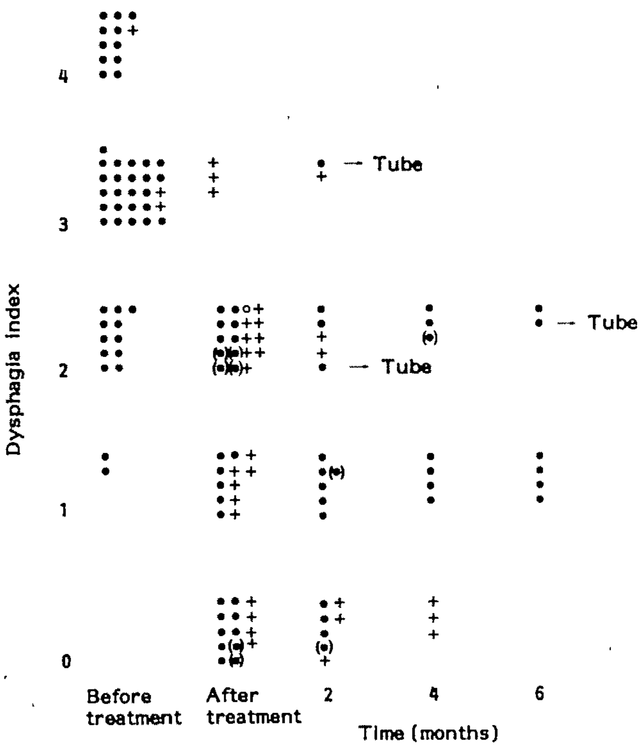

Figure 2 *Long-term results of laser treatment. Dysphagia index assessed as ability to swallow 0, all foods, 1, most solids, 2, semisolids, 3, fluids; 4, total dysphagia.* ●, *Individual patients,* (●), *patient alive but has not reached next stage;* O, *patient refused follow-up,* +, *death before completing the next stage. Position of cross shows the dysphagia index at the last completed stage before death. At death most patients were taking a solid or semisolid diet*

There was one perforation due to dilatation and one suspected perforation due to the laser in this series. Symptoms of reflux oesophagitis were common and Gaviscon® (Reckitt and Colman, Hull, UK) treatment was helpful.

Discussion

Both palliative and 'curative' surgery for carcinoma of the oesophagus carry high risks of morbidity and mortality and 80 per cent of patients are dead within 1 year[5]. Our results suggest that good palliation of dysphagia with minimal morbidity and mortality can be achieved with the laser and are in agreement with data from other workers[6-8]. Not all patients can be kept swallowing with laser therapy and 6 per cent required intubation in this series. In one patient satisfactory swallowing was maintained for 6 months before intubation became necessary.

A major problem in this condition is the impassable stricture. In these cases direct contact laser therapy offers a good method of opening up the stricture. This is in agreement with results from a previous study[9] but in our hands does not require a general anaesthetic.

In conclusion the laser offers a safe method of palliation in patients with malignant obstruction of the oesophagus. As the results of surgery for carcinoma at this site are so poor we would recommend that patients fit for surgery are initially assessed using a computed tomographic scan[10]; those shown to have advanced disease on scanning, elderly patients and those unfit for surgery are best treated by laser therapy.

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Changing patterns in gastric adenocarcinoma

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A retrospective study was performed on gastric cancer patients admitted to the Cancer Institute Hospital, Tokyo, during the periods 1961–65 (n = *1181*) *and 1980–84* (n = *1473*)*. The aim of the study was to see whether changes had occurred in gastric cancer patients over the years with respect to histology and tumour localization and, if so, how they compared with reports from the West. The proportion of proximally localized primary tumour increased from 17 to 27 per cent* ($P=0{\cdot}008$)*, and signet-ring cell carcinoma increased from 2 to 22 per cent* ($P<0{\cdot}001$)*. These changes were not relative with regard to the declining incidence of intestinal tumours, but absolute. Patients with proximally localized tumours were generally in a more advanced stage of disease than those with distally localized tumours, and thus had poorer survival rates. However, after stratifying into stages, the difference in survival disappeared. The survival rate of patients with signet-ring cell carcinoma was not significantly different from that of patients with other gastric tumours* ($P>0{\cdot}05$)*. The discrepancy between the survival rates of Japanese and western gastric cancer patients is attributed by some authors to tumour-related factors. However, we believe that the similar trends found with regard to tumour localization and histology point towards comparable tumour behaviour in the two different geographical areas.*

Keywords: Gastric carcinoma, histology of gastric cancer, tumour localization in gastric cancer, tumour behaviour

It is well established world-wide that the incidence of gastric cancer is declining but this trend has been observed only recently in Japan. Other trends are occurring and several reports from western countries indicate changes in the localization and histology of gastric adenocarcinoma[1–5]. The incidence of tumours in the proximal stomach seems to have increased in comparison with distal locations. A reason for this has not yet been found, but it has been suggested that if the intestinal form of adenocarcinoma, which occurs most often in the distal stomach, is decreasing, this would cause a relative change. Changes in histology have also been observed when comparing data from the 1950s and the 1980s[2,3]. Recent studies report a higher incidence of signet-ring cell carcinoma.

We considered that these trends were important when attempting to identify any differences in the features of gastric cancer in Japan compared with the West. The present study was mounted at the Cancer Institute Hospital, Tokyo, to describe changes in Japan and to determine whether the biological behaviour of tumours explains the discrepancy in survival results between Japan and the West.

Patients and methods

All patients who underwent an operation for gastric cancer in the Cancer Institute Hospital, Tokyo, during the two 5-year periods 1961–65 ($n=1181$) and 1980–84 ($n=1473$) were reviewed. In 145 and 77 patients, respectively, some histological data were missing because only laparotomy or bypass anastomosis was performed. These patients were excluded from the analysis leaving 1036 and 1396 patients in the study.

Localization

Firstly, all patients, early as well as advanced cases, were analysed for tumour localization and stage of disease; the mean age and the male:female ratio were calculated. Patients were classified according to tumour localization as follows: C, upper third; M, middle third, A, lower third of the stomach. The upper division line was set 5 cm distal to the oesophageogastric junction. As we wished to make a comparison with western reports, a separate analysis was done of patients with advanced gastric cancer, i.e. tumour invasion beyond the submucosa. Tumour localization, mean age and male:female ratio were again determined for the two periods and a further analysis was performed.

Histology

Patients with advanced gastric cancer from both groups were analysed with regard to the histological reports All specimens had been examined histologically at the Department of Pathology of the Cancer Institute Hospital, Tokyo. Patients were placed into categories on the basis of the following histology: well differentiated, poorly differentiated, and signet-ring cell adenocarcinoma. Other types of histology were ruled out. The diagnosis of signet-ring cell carcinoma was made if more than 50 per cent of the tumour cells were characteristic, i.e. numerous mucin vacuoles that may distend cells or may coalesce and compress the flattened nucleus against the plasma membrane. The criteria were not changed during the periods in question. For those patients with signet-ring cell carcinoma, age, sex distribution and localization of primary tumour were determined separately for the two periods, and then compared.

Statistics

χ^2 analyses were employed for the comparison of individual variables. The patients operated on from 1980 to 1984 were stratified in stage groups according to the new TNM (UICC tumour node metastasis) system. To establish any relationship between location or signet-ring cell carcinoma and stage of disease, the proportion of patients with C location and signet ring cell carcinoma was calculated as a percentage of the entire group of 1980–84 patients, including patients with early as well as those with advanced gastric cancer Surgical mortality was defined as death within 30 days of operation.

Results

An increase in the proportion of early gastric cancers was seen in the second period (*Table 1*), in most cases these occurred in the body of the stomach. Age and male:female ratio did not change significantly between the two periods ($P>0{\cdot}05$ and $P>0{\cdot}1$ respectively).

All early gastric cancer patients (i.e. tumour restricted to the (sub)mucosa independent of lymph node involvement[7]) were then excluded, leaving two groups of patients with advanced cancer for further analysis; there were 865 and 811 patients from the 1961–65 and 1980–84 periods respectively. The incidence of proximally situated advanced gastric

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Table 1 *Depth of invasion, age and sex ratio of patients operated on for gastric cancer in two periods, 1961–65 and 1980–84*

	Operation period	
	1961–65 (*n*=1036)	1980–84 (*n*=1396)
Age (years)		
Mean	55·8	56·2
Median	57·2	58·1
Sex (M:F ratio)	1·76	1·93
Early cancer	171 (16·5)	585 (41·9)
Advanced cancer	865 (83·5)	811 (58·1)

Values in parentheses are percentages

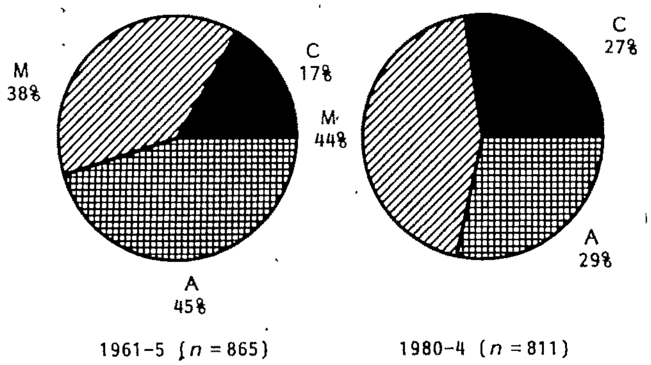

Figure 1 *Location of advanced gastric cancer in the two periods. C, upper third; M, middle third; A, lower third*

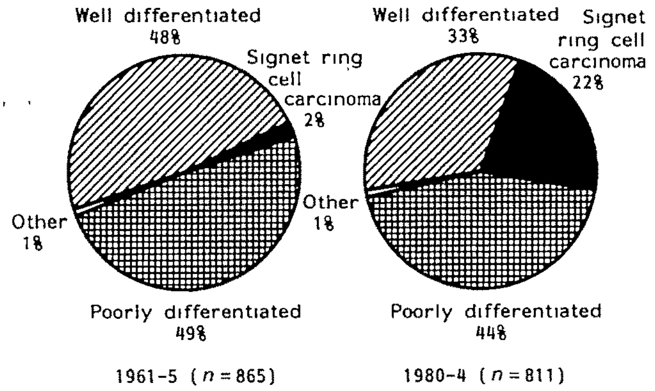

Figure 2 *Histology of advanced gastric cancer in the two time periods*

adenocarcinoma increased from 17 to 27 per cent, which is a statistically significant change (*Figure 1*; $P=0{\cdot}008$). The mean age of patients with advanced disease increased from 55·4 years (median 57·2 years) to 58·1 years (median 59·6 years; $P=0{\cdot}1$) and the male:female ratio decreased from 2·43 to 1·96 ($P=0{\cdot}08$).

Subsequently we compared the histological results between the two groups of patients with advanced gastric cancer. Signet-ring cell carcinoma was diagnosed in 2 per cent ($n=19$) of the patients in the first period and in 22 per cent ($n=178$) in the second period (*Figure 2*; $P=0{\cdot}0001$). Although the group of patients with signet-ring cell carcinoma was too small to make a reliable statistical calculation, it seemed that the mean age within this group had decreased from 57·2 to 51·7 years ($P>0{\cdot}05$). The male:female ratio change was not significant, rising from 0·73 to 0·94 ($P>0{\cdot}05$).

Figures 3 and *4* show the stage grouping for C location and signet-ring cell carcinoma for the period 1980–84. Proximally located tumours were generally diagnosed in a more advanced stage of disease than distally located tumours and thus have poorer survival rates. The operative mortality rate was 0·87 per cent in the group with proximally located cancer, compared with 0·45 per cent in those with more distally localized tumours. There was no relationship between histology and the stage of disease in patients with signet-ring cell carcinoma (*Figure 4*).

Discussion

Proximally located gastric cancer has been diagnosed more frequently in recent years; an average increase from 10 per cent to 40 per cent has been reported in the last three decades[2–4]. In the present study, it was decided to exclude early gastric cancer patients from the analysis for two reasons: firstly, in western and other 'low incidence' countries, where double contrast radiographs and gastroscopy are not used as frequently as in Japan, only 2–6 per cent of diagnosed cases are early gastric cancers, whereas in Japan early gastric cancer accounts for 41 per cent of the cases[1,5]. Secondly, as reported by Sasse *et al.*[5], and confirmed in our study, early gastric cancer is detected relatively less frequently in the proximal stomach than in more distal locations. However, it cannot be concluded that early gastric cancer is merely confined to distal locations, as the determination of early gastric cancer in the proximal stomach is technically difficult[8]. Therefore, an analysis using only patients with advanced cancer will exclude any bias caused by detection problems and thus be more comparable with western reports.

In the Cancer Institute Hospital, Tokyo, we have also found

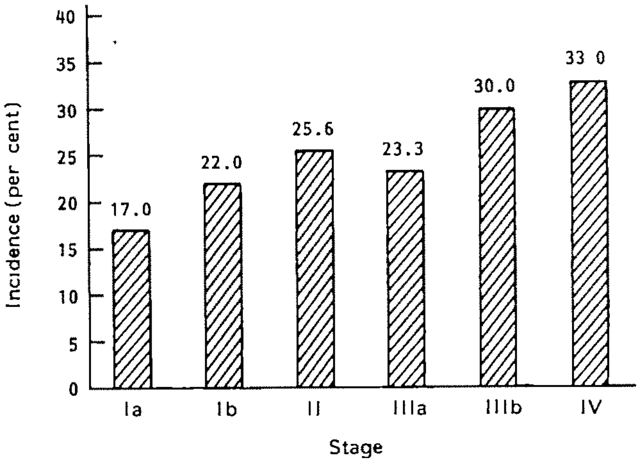

Figure 3 *Relationship between stage of gastric cancer and incidence of upper third location. The exact percentages are given for each stage*

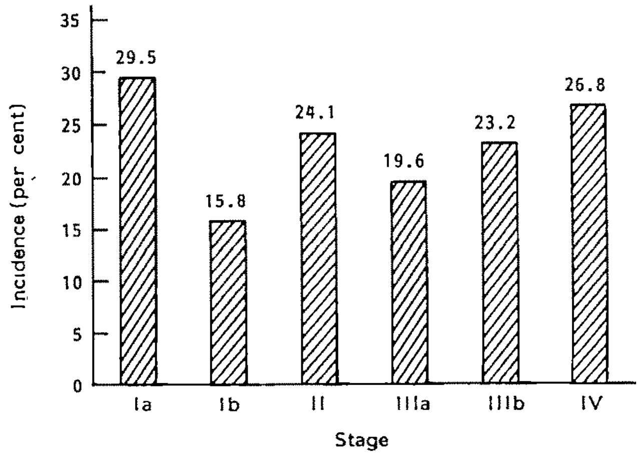

Figure 4 *Relationship between stage of gastric cancer and incidence of signet-ring cell carcinoma. The exact percentages are given for each stage*

an increased incidence of proximally located cancer, although the change is not as marked as in western series. So far no explanation has been found. Two previous reviews[4,5] suggest that it is a matter of relative change, as the incidence of distal, intestinal type tumour[6] is declining. We also observed a decreased incidence of antral tumours from 45 to 29 per cent, but the increase of proximally located tumour was absolute, rising from 144 to 222 cases (from 17 to 27 per cent) despite a small fall in the population of patients with advanced gastric cancer. Meyers *et al.*[3] suggested that specific dietary carcinogens may induce cancer at different locations. Although diet certainly influences the occurrence of gastric cancer, no evidence has been offered as yet to support specific, location-bound induction within the stomach. Another hypothesis is that of inherited genetic susceptibility, an hypothesis supported by observed racial differences[9]. In our study all patients were from a homogeneous occidental population, and therefore we were unable to examine this proposal. The male:female ratio decreased to about 2·0, which is in contrast with several publications that report a far greater male predominance[1,2] The increased mean age of 58·1 years in the second period corresponds with that reported in other publications[1–3].

The second change in gastric cancer was the observation of a higher incidence of signet-ring cell carcinoma. The diagnosis is, in part, dependent on two subjective judgements. Firstly, the more advanced the tumour, the more difficult it is to make a definite diagnosis; the characteristic mucin and trabecular system seem to be less clear the more the tumour invades the gastric wall[10]. Secondly, the decision to make the diagnosis of signet-ring cell carcinoma depends on the percentage of characteristic tumour cells that is set as a criterion by the individual pathologist. If we overlook these definition problems, an increasing number of patients with signet-ring cell carcinoma has been noted[2]. By setting the criterion for diagnosis at 50 per cent characteristic cells, we also found a significant increase (of up to 22 per cent) in the proportion of signet-ring cell carcinomas and a predominance in distal locations. The male:female ratio did not change significantly, but was low when compared with other publications.

Our study shows that patients with proximal gastric cancer have a worse prognosis than those with a more distally located tumour. However, after stratification the difference disappears, implying that proximally located tumours are generally found at a later stage of disease. This agrees fully with the concept that detection of early cancer in the proximal stomach is mainly a technical problem. For signet-ring cell carcinoma, the survival rates were not statistically different from those of patients with poorly or well differentiated adenocarcinoma. This agrees with the study of prognostic factors in gastric cancer by Maruyama and Miwa[11], in which histology is awarded a relative risk factor of only 1·16 using Cox's proportional hazards model. On the other hand, some signet-ring cell carcinomas may be of parietal origin, carcinomas that are thought to carry a different prognosis.

In conclusion, we have found similar trends in the gastric adenocarcinoma patients at the Cancer Institute Hospital, Tokyo, as have been found in several western populations. It would be more appropriate to compare population-based data but, from the present study, it seems that similar trends in localization and histology are occurring in gastric cancer patients, in low- as well as high-incidence countries.

Acknowledgements

The author would like to thank Dr M Nishi, President of the National Cancer Institute Hospital, Tokyo, for his contribution to the study.

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Late perforation of a mediastinal oesophagocoloplasty

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Perforation of a colonic interposition for oesophageal stenosis has not been previously reported after ingestion of aspirin. We present a patient in whom conservative management was successful.

Case report

A 33-year-old man with a long-standing history of oesophageal stenosis due to gastroesophageal reflux and four previously unsuccessful operations, underwent resection of the oesophageal stenosis with a left isoperistaltic coloplasty in 1979. In June 1988 the patient was involved in an accident while manipulating a fire-work rocket. As a result, he developed a painful lesion in the left hand and started taking analgesics (2–4 g/day acetylsalicylic acid). In August he noticed the acute onset of epigastric discomfort and pain in the right posterior hemithorax; 7 days before admission he passed black-tarry stools.

On admission the patient was haemodynamically stable, with epigastric pain. Rectal examination confirmed black-tarry stools. The haemoglobin was 9·5 g/dl and the white blood count $9{\cdot}5 \times 10^3$/dl. The electrocardiogram showed a sinus tachycardia of 160 beats/min. The chest X-ray showed surgical changes in the right hemithorax, while the plain abdominal films were normal. Twelve hours later severe respiratory distress developed with a fever of 39·5°C. He was admitted to the intensive care unit. Chest X-ray revealed an infiltration in the right lung, and a rise in the white cell count ($12{\cdot}2 \times 10^3$/dl) was noted. Seventy-two hours later there was evidence of progressive lung consolidation with cavitary lesions in the pleural space and mediastinum that were confirmed by computed tomographic (CT) scan. A barium swallow showed a leak in the lower third of the intrathoracic colon, with free barium above the right hemidiaphragm (*Figure 1*). An upper gastrointestinal endoscopy showed abundant pus and mucus in the colonic mucosa but the perforation could not be visualized.

Antibiotic therapy was started with clindamycin and tobramycin, and parenteral nutrition was initiated. A large chest tube was placed under CT scan guidance in the largest cavity, but the fever persisted and a repeat CT scan revealed another large posterior cavity; this was also drained percutaneously. His clinical condition improved subsequently, and a further Gastrographin® (Schering, Berlin, GDR) swallow showed no evidence of leakage. On day 45 the chest tubes were removed and oral feeding was started.

Discussion

The development of fistulae in oesophageal surgery is a common complication in the postoperative period[1] but the late presentation in this case is a rare finding[2]. The most probable cause was the development of an ulcerative lesion in the colonic mucosa, secondary to the massive intake of aspirin. The ulcer was not seen on endoscopy but it seems reasonable to assume that the erosive effect of salicylates[3], potentiated by the stasis that frequently occurs after a coloplasty[4], triggered perforation in the colonic mucosa. The clinical picture of pain and upper gastrointestinal bleeding, followed by the development of intrathoracic leakage with pleural and mediastinal abscesses, substantiates this hypothesis.

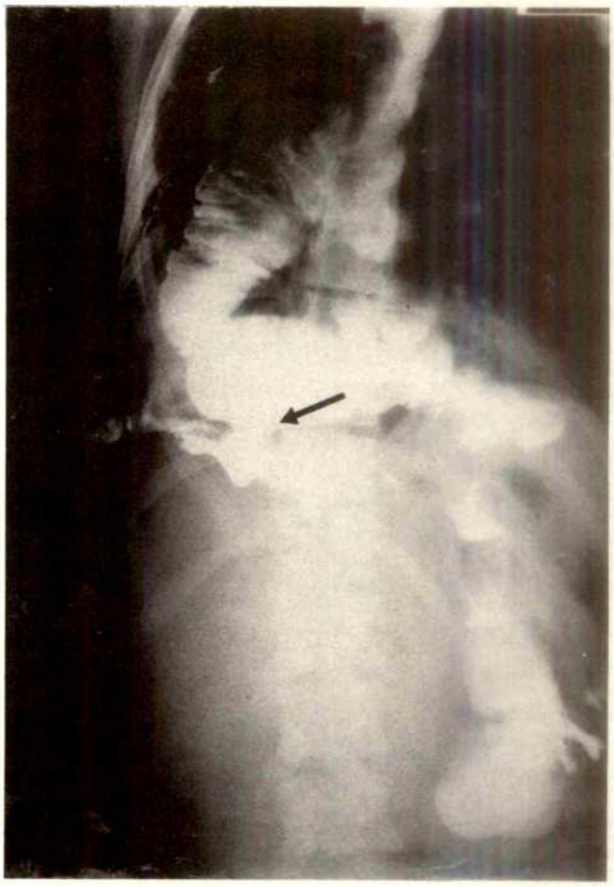

Figure 1 *Barium extravasation from coloplasty with contrast medium above the right hemidiaphragm (arrow)*

The early introduction of parenteral feeding and the percutaneous drainage of the thoracic purulent collections with appropriate antibiotic cover were followed by a remarkable clinical improvement and resolution. We believe that this conservative approach spared the patient a complicated surgical procedure, the outcome of which was uncertain because of his critical condition and previous history of multiple thoracic and abdominal operations.

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Emergency subtotal oesophagectomy

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From 1981 to 1987 nine patients have undergone resection and reconstruction of the oesophagus as an emergency, using a two-part left-sided approach with oesophagogastric anastomosis in the neck. Five patients had oesophageal perforation with a carcinoma; one had spontaneous perforation of an intrathoracic stomach; two had severe haemorrhage; and one had acute sterile mediastinitis. Following operation there was one postoperative death (11 per cent) and no major complications. Long-term survival was marred only by the development of further malignancy in four patients. Subtotal oesophagectomy has both theoretical and practical advantages over conventional oesophagogastrectomy in oesophageal emergencies and we suggest that it should be considered as the method of choice in the management of these difficult cases.

Keywords: Oesophageal perforations, carcinoma, resection

Management of the patient who requires oesophageal resection as an emergency presents a number of singular and sometimes refractory difficulties. Such patients are frequently in shock, with gross pleural or mediastinal contamination from oesophageal leaks, and some are elderly and have significant associated cardiac or pulmonary disease. Frequently, the oesophageal diagnosis is incomplete, particularly with respect to the presence or absence, nature and extent of pre-existing conditions (such as tumour, stricture or motility disorders), and even the size and location of perforations may not have been clearly defined.

In these circumstances the surgical approach must make it possible to deal with a wide variety of operative findings, and we have therefore preferred a two-part left-sided subtotal oesophagectomy with cervical oesophagogastric anastomosis, as recently described for the elective resection of oesophageal carcinoma[1]. In the past 7 years we have used this procedure on nine critically ill patients in our unit, and the purpose of this paper is to present our results and discuss the merits of this approach in the treatment of oesophageal emergencies requiring resection.

Patients and methods

From January 1981 to December 1987 a total of 318 oesophageal resections were performed under the care of the senior author (H.R.M.), of which nine (2·8 per cent) were done as an emergency. The ages of the patients ranged from 27 to 71 years (mean 54 years) and six were men; clinical features are summarized in *Table 1*.

Six patients had gross mediastinal and pleural contamination from intrathoracic leaks. Five of these were the result of endoscopic perforation (four from outside units, one from our own) and all had an underlying carcinoma, although this was not recognized until operation in two patients. The sixth patient had undergone an intrathoracic Nissen fundoplication for short oesophagus and reflux stricture 3 months previously at another hospital and was admitted in profound shock with spontaneous necrosis and perforation of the gastric fundus into the left chest. Owing to delays in diagnosis and transfer to our unit, three of these patients were not operated on until 24 h after the perforation, the others being operated on at 8, 12 and 14 h respectively; for this group of six patients the mean interval from perforation to operation was 18 h.

Two patients were resected for severe haemorrhage. The first of these (No. 7) had oesophageal varices and portal hypertension from chronic active hepatitis B and had been treated by sclerotherapy for recurrent bleeding on at least ten occasions during the preceding 14 months. He was admitted on this occasion with further severe bleeding which failed to respond to treatment, including the use of a Sengstaken–Blakemore tube. He had already been referred to another hospital for possible oesophageal transection but was considered to be unsuitable for this because of dense oesophageal fibrosis from his repeated sclerotherapy, and oesophageal resection was therefore preferred. The second patient (No. 8) was admitted with acute haemorrhage from a Barrett's ulcer in a columnar-lined oesophagus, with associated hiatus hernia and gastro-oesophageal reflux; conservative treatment was unsuccessful and operation was performed after transfusion of 13 units of blood.

The remaining patient (No. 9) presented an unusual problem: having been perfectly well for 3 days after oesophagoscopy and dilatation for chronic oesophageal ulceration and stricture he suddenly developed severe central chest pain and vomiting, with shock. A postemetic rupture was suspected but a Dionosil® (Glaxo Laboratories Ltd., Greenford, UK) swallow showed no evidence of rupture or perforation, and exploration was performed. This revealed a chronic penetrating ulcer which was densely adherent to the mediastinal connective tissue with an associated short oesophagus and reflux stricture. There was no free perforation of this ulcer but the mediastinal tissues around it were grossly oedematous. It was postulated that the original dilatation of the stricture may have aggravated the reflux, leading to inflammation in the base of the ulcer and an acute sterile mediastinitis.

Excluded from this study are 12 patients with intrathoracic perforation of the oesophagus who were seen during the same time period but who were managed without resection. Three of these patients (with terminal carcinoma) received no active treatment, eight were treated by conservative means, with or without chest drainage, and one was treated by operative repair.

Perioperative management

Before operation all patients received intravenous fluids (electrolyte, colloid or blood) and one required vasopressors, but operation was not delayed even if a normal circulation could not be restored. Antibiotics were administered before operation in the six patients with leaks, and at the time of induction of anaesthesia in the other three patients. Radiological contrast studies were obtained as an emergency in five patients, but were omitted in two patients who were too ill and in the two bleeding patients who had already had them. Emergency endoscopy was not performed in any patient, but the chest was drained before induction of anaesthesia in all patients with a pneumothorax or hydrothorax.

Subtotal oesophagectomy was performed in all patients through a left thoracolaparotomy in the sixth intercostal space, followed by an oblique left cervical incision, as previously described[1]. After mobilization of the thoracic oesophagus the cardia was divided and closed and the stomach was mobilized fully, preserving only the right gastroepiploic vessels and their associated arcades. Posterior pyloromyotomy was performed for gastric drainage and the elongated stomach was then positioned in the mediastinum, medial to the aortic arch and up to the apex of the chest, with end-to-end anastomosis of the stump of the oesophagus to the fundus of the stomach through the cervical incision. Two patients were found to have complicating factors in the form of a benign gastric ulcer in one case and a colloid goitre in another, but neither of these prevented satisfactory completion of the operation.

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Table 1 *Clinical features of patients having emergency subtotal oesophagectomy from 1981 to 1987*

Patient no.	Age (years)	Sex	Pre-existing condition	Emergency indication	Time from perforation to operation (h)	In-hospital stay (days)	Outcome
1	67	M	Adenocarcinoma cardia Node positive	Endoscopic perforation (rigid)	24	27	Died at 8 months Recurrence
2	71	F	Squamous carcinoma lower third Node negative	Endoscopic perforation (flexible)	24	24	Died at 4 years 9 months Primary pelvic adenocarcinoma
3	48	F	Squamous carcinoma middle third Node positive	Endoscopic perforation (flexible)	24	—	Died on third postoperative day
4	53	F	Squamous carcinoma middle third Node negative	Endoscopic perforation (flexible)	8	11	Alive at 2 years 7 months Recurrence
5	48	M	Adenocarcinoma lower third Node negative	Endoscopic perforation (rigid)	14	14	Alive and well at 9 months
6	42	M	Intrathoracic Nissen fundoplication	Spontaneous intrathoracic gastric perforation	12	23	Alive and well at 2 years
7	27	M	Oesophageal varices, portal hypertension	Haemorrhage	—	10	Alive and well at 2 years No further bleeds
8	66	M	Barrett's ulcer, columnar-lined oesophagus	Haemorrhage	—	22	Died at 2 months Malignant hepatoma
9	60	M	Penetrating ulcer, hiatus hernia, reflux	Acute sterile mediastinitis	—	16	Alive and well at 9 months

One patient (No. 6) had to have an area of gastric necrosis adjacent to the cardia resected with a cuff of stomach, but gastric resection was not performed in any other patient. In the patient with oesophageal varices (No. 7) splenectomy was performed for a grossly enlarged spleen.

After operation, patients were ventilated only if their spontaneous respiration was unsatisfactory. Nasogastric tubes were not used in any patient, but one (No. 6) had a small Foley catheter inserted across the neck, as a temporary gastrostomy, to decompress the stomach which was severely inflamed. Oral fluids were commenced from the second postoperative day, as soon as the patients' general condition permitted, and they then progressed to soft diet by the time of discharge from hospital. Parenteral nutrition was not routinely employed. Antibiotics were continued after operation in those patients who had intrathoracic contamination at the time of surgery.

Results

Early results (Table 1)

Of the nine patients, eight made a satisfactory recovery and one (No. 3) died on the third postoperative day from renal failure and irreversible shock, having required vasopressors even before operation. Autopsy by the coroner's pathologist confirmed death from circulatory failure with no evidence of residual tumour; the oesophagogastric reconstruction was healthy and intact. Two patients required ventilation for 3 and 11 days respectively (the latter requiring tracheostomy) and one patient developed sputum retention on the second postoperative day and was treated by minitracheotomy and high-frequency jet ventilation[2] for 8 days with a good recovery. One patient was found to have a localized anastomotic leak on routine postoperative barium studies but was asymptomatic and no treatment was required. No other complications occurred. Inpatient stay ranged from 10 to 27 days with a mean of 18 days.

Late results (Table 1)

Of the four surviving patients with perforated carcinoma, one died at 8 months from recurrence, one died at 4 years and 9 months from a primary pelvic tumour (of different histological type), one is alive at 2 years 7 months with recurrence, and one is alive and well at 9 months. Of the patients with non-malignant disease, one died at 2 months from a primary hepatoma that was not diagnosed at the time of operation, and the remaining three are alive and well from 9 months to 2 years after operation. One patient had temporary mild dysphagia which required anastomotic dilatation, but no other complications referable to the operation have developed and no surgical revision has been required.

Discussion

In this paper our main concern has been with the management of those oesophageal emergencies that are bad enough to require immediate resection. It is well recognized that some cases of oesophageal perforation, for example, can be treated successfully without resection, but this is generally not the case when there is carcinoma and a free connection between the oesophageal lumen and the pleura, as in five of the six patients with perforation in this series. In these cases the principle of immediate resection and reconstruction has become well established since the first such procedure was reported by Satinsky and Kron[3,4], although initial resection (with oesophagostomy and gastrostomy) followed by delayed reconstruction may be safer in late cases with gross mediastinal infection[5,6].

Most of the immediate resections and reconstructions reported, however, have consisted of a conventional oesophagogastrectomy, removing only the lower oesophagus and upper stomach, with an intrathoracic anastomosis below the level of the aortic arch. While the results with this procedure have generally been reasonably satisfactory it does have certain limitations. Firstly, it does not give very good lymphatic clearance in patients with carcinoma; secondly, in cases with mediastinitis the anastomosis has to be constructed using inflamed oesophagus in a potentially infected field, which may well predispose to serious postoperative leaks[7]; thirdly, if patients do survive long-term then they are liable to have significant symptoms or complications from reflux[4]; and fourthly, the procedure is not suitable for lesions higher in the oesophagus.

Oesophagogastric anastomosis in the neck overcomes these difficulties. Longitudinal clearance of tumours is clearly better, which may improve the prospects for long-term survival[1], and the anastomosis is constructed in a relatively clean field using healthy proximal oesophagus, which is well vascularized and not oedematous or inflamed. Reflux is less likely to occur than with an intrathoracic anastomosis because of more favourable transanastomotic pressure relationships[8], and the procedure is applicable to lesions at any level in the thoracic oesophagus. From the technical point of view anastomosis in the neck is actually easier than in the chest, as the two ends are delivered and joined outside the cervical wound and not at the bottom of a deep thoracic cavity. In our patients we found no difficulty in getting the stomach to reach to the neck, despite the presence of a gastric ulcer in one patient and a gastric perforation in another, and the use of a cervical anastomosis did not increase the length of the operation as the intrathoracic part was correspondingly shorter.

In a few patients supra-aortic or 'high' intrathoracic anastomoses have been reported, using stomach[3,9,10] or colon[11], and Larsson and Pettersson[5] have stressed the importance of a high anastomosis in diminishing postoperative reflux, but the routine use of a cervical anastomosis for emergency resections has not apparently been proposed. Our results would suggest that such a policy merits serious consideration. Apart from one postoperative death from irreversible shock, the early results have been excellent and the long-term outcome has been marred only by the development of further malignancy (either primary or secondary). In some circumstances (e.g. late cases with gross infection) immediate reconstruction is not advisable, and the neck should be opened to construct a terminal oesophagostomy and defunction the mediastinum. In cases that are suitable for immediate resection and reconstruction, we would suggest that the neck should be used as the preferred site for the construction of the anastomosis.

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Laser angioplasty with a pulsed NdYAG laser: early clinical experience

Since December 1986, 40 laser angioplasty procedures have been performed using the energy from a pulsed NdYAG laser, delivering near infrared light (1064 nm) in 100-μs pulses of approximately 300 mJ per pulse, directly through a transparent sapphire tipped device. All patients had total occlusion of the superficial femoral artery and symptoms severe enough to warrant surgery, with ulceration or gangrene in eight, rest pain in 14 and severe claudication interfering with life-style in the others. The device was introduced through an antegrade puncture of the superficial or common femoral artery and laser recanalization was followed by attempted balloon angioplasty in all cases. Occlusions were a median length of 15 cm (range 2–35 cm); ten patients had previously undergone failed attempts at conventional balloon angioplasty and four had occluded femoropopliteal grafts. Thirty-seven legs of 34 patients were treated with an average of 60 J (range 10–235 J) with successful recanalization in 27 and immediate reocclusion in seven. The 20 successful recanalizations have been followed up for up to 24 months (median 7 months) with only one late occlusion at 5 months. Failed recanalization was due to poor transmission by the delivery device in the early part of the series (five cases), repeated passage of the device down a collateral branch (four cases), dissection at the site of previous surgery (two cases) or no apparent reason (two cases). Immediate reocclusion was due to very poor run off in patients with severely ischaemic limbs (three cases) or technical difficulties with balloon dilatation (two cases). Complete symptomatic relief was obtained in all the cases of radiologically successful laser angioplasty. Early surgery was required in one case following reocclusion of the artery when an angioplasty balloon failed to deflate, and one patient suffered a skin reaction thought to be due to inadequate removal of the sterilizing solution. A different sterilizing procedure is now followed. Laser angioplasty can reduce the number of patients requiring bypass surgery and improvements in the device and access methods may reduce the number of untreatable cases.

Keywords: Laser surgery, atherosclerosis, balloon angioplasty, laser angioplasty, peripheral vascular disease

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The development of laser and fibreoptic technology has made it possible to deliver intense energy, in the form of light, through narrow flexible fibres. This enables the surgeon to unblock occluded arteries by delivering laser energy percutaneously through a narrow fibre. Early work using a bare fibre, although successful, produced an unacceptable rate of vessel perforation[1], so that methods of modifying the delivery device have been sought. The first device to obtain approval for clinical use consisted of a metal probe, heated by energy from a continuous wave laser[2], and this has now been used with some success in the peripheral circulation[3]. However, recent experimental evidence suggests that debris formation may be a problem with such a device[4], which may explain the poor results of the small number of reported cases in which it has been used in the coronary circulation[5].

Theoretical and experimental work has shown that short pulses of laser energy, delivered directly to tissue, result in the ablation of tissue with little surrounding thermal damage[6,7]. Optical devices are now available which can delivery such pulsed energy into a blocked artery without becoming hot and attracting the clot and debris which develop on the metal probe[8,9].

The results and initial follow-up are reported for the first clinical series in which a pulsed laser has been used, via a percutaneous approach, to recanalize occlusion of the superficial femoral artery.

Patients and methods

A total of 40 laser procedures have been performed on 37 legs of 34 patients with severe symptoms of peripheral vascular disease due to complete occlusion of the superficial femoral artery. Initially, laser treatment was only considered for patients with threatened limb loss in whom all other possible treatment options had been attempted or were considered inappropriate. After the first 12 procedures, the indications were relaxed to include any patient who had a clinical indication for vascular surgery with a lesion amenable to laser treatment. All patients with femoropopliteal disease were considered unless: (1) there was evidence of recent sudden deterioration in condition suggestive of an acute occlusion, or (2) adequate access to the superficial femoral artery could not be achieved.

Twenty-six men and eight women with a median age of 69 years (range 37–87) were treated, the right leg being treated in 17 and the left leg in 20 cases; 12 were treated for severe claudication, 14 for rest pain and eight for ulceration or gangrene. Four patients had undergone

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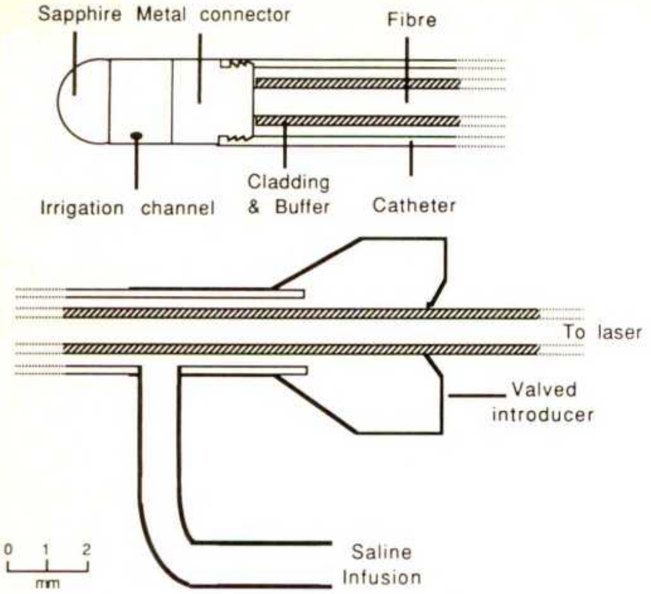

Figure 1 *Diagram of the catheter with an artificial sapphire tip as used for clinical laser angioplasty*

previous femoropopliteal bypass and ten had previous failed attempts at balloon angioplasty on the treated leg. The median (range) ankle:brachial pressure index (ABPI) was 0·6 (0·3–0·7) at rest and 0·2 (0–0·5) after exercise in the claudicants and 0·3 (0–0·7) at rest in those with rest pain or gangrene. All had total occlusion of the superficial femoral artery with a median length of 15 cm (range 2–35 cm); seven had a superficial femoral stump of less than 2 cm, and in three of these there was no stump visible on angiography. Poor run off was not considered a contraindication to treatment; there was an average of two run-off vessels, with three of the treated patients having an isolated popliteal segment. Two patients had evidence of ipsilateral iliac stenosis and these were treated by balloon dilatation before considering laser angioplasty.

There was a high incidence of coexisting disease, such as coronary heart disease, cerebrovascular disease and diabetes mellitus, and most patients were considered a poor risk for general anaesthesia.

Laser angioplasty was carried out with a pulsed NdYAG laser (Lumonics Ltd., Rugby, UK) delivering light in the near infrared at a wavelength of 1064 nm. Pulses of 100 μs duration at a repetition rate of 10 Hz are delivered through a 600-μm core diameter optical fibre with a 2·2-mm diameter hemispherical tip made of sapphire (Surgical Laser Technologies (UK) Ltd., Keighley, UK). The sapphire is mounted on a catheter using a metal connector with a side hole through which normal saline is infused (*Figure 1*). The system delivers between 250 and 350 mJ per pulse, giving an average power at 10 Hz of 2·5–3·5 W. The power output was measured at the beginning of each procedure and the timer set to deliver a series of pulses totalling 5 J (i.e. 1·4–2·0 s).

All lesions were approached through an antegrade puncture of the ipsilateral common or superficial femoral artery under local anaesthesia. A 7 or 8 Fr valved introducer sheath was placed in the superficial femoral vessel and preliminary angiography performed. The site of the upper and lower ends of the occlusion were marked and heparin (5000–10 000 units) was given through the sheath. Saline was infused through the angioplasty device at a pressure of 300 mmHg and rate of 4 ml/min. The device was introduced to the upper end of the occlusion under radiological control, advanced gently until resistance was met and exposures of 5 J were repeated until the occlusion was crossed. The laser fibre was replaced with a guidewire, a catheter was introduced through the occlusion and contrast was injected to demonstrate the integrity of the distal vessels. Balloon angioplasty was then performed working from the distal end of the reopened segment of artery with two inflations to 8 atm (811 kPa), at each overlapping site (*Figure 2*).

Completion angiography was performed and haemostasis secured at the groin puncture site. After 24 h bed rest the patient was mobilized and discharged from hospital on aspirin and dipyridamole. Progress was assessed by symptoms, clinical examination, and by the measurement of ABPI before the procedure and during the follow-up period. Angiography was not repeated routinely but was performed if there was clinical indication.

Results

Of the 40 attempted procedures on 37 legs there was successful recanalization of the superficial femoral vessel in 27. Three repeat procedures were carried out after failures due to device problems and two of these were unsuccessful on the second attempt. None of those patients in whom there was a failure of recanalization suffered from any deterioration in the clinical or radiological severity of their disease and most of those in whom surgery was feasible went on to have the vascular surgery that was originally planned. The reasons for failure of recanalization were evident in most cases. In five there was found to be poor output from the laser device: two were related to fibre damage and three were carried out with a sapphire of different geometry that was found to transmit less energy and produce more heat than the usual sapphire. Four failed recanalizations were due to an inability to reach the site of occlusion because of repeated passage of the device down a side-branch at the upper end of the blockage. Two were due to dissection at the site of anastomosis of a previous suprageniculate bypass graft and two others failed for no apparent reason.

An average of 60 J (range 10–235 J) was required for recanalization and the procedure was tolerated well. Pain

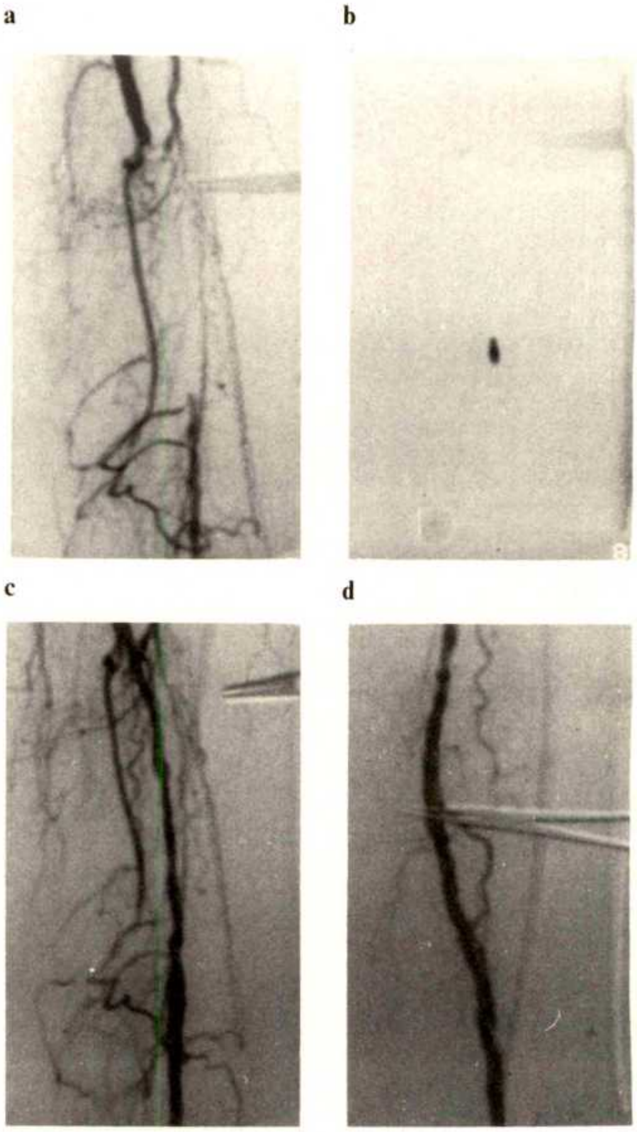

Figure 2 *Digital subtraction angiography showing a laser angioplasty procedure:* **a** *an occlusion of the superficial femoral artery before treatment;* **b** *the sapphire tip advancing through the occlusion;* **c** *the narrow channel following laser recanalization; and* **d** *the channel following balloon dilatation*

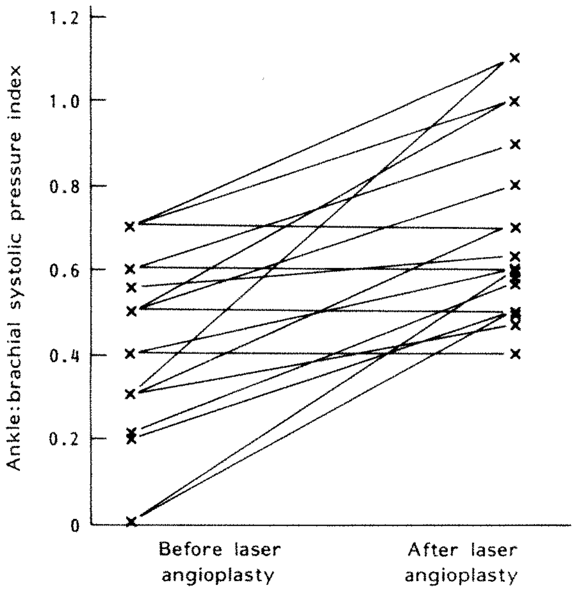

Figure 3 *Ankle:brachial systolic pressure index before and after laser recanalization in 18 patients with radiological success for whom data were available*

during laser exposure occurred in a few cases and was not severe but was sometimes associated with vessel dissection and was therefore taken as an indication to stop laser exposure and repeat the angiogram.

Of the 27 recanalized vessels, balloon dilatation was performed in 26, the exception being a case in which the guidewire repeatedly passed down a collateral vessel rather than through the channel made by the laser. Despite the lack of balloon dilatation the symptoms improved and the vessel remains patent at 17 months.

In seven cases the vessel reoccluded at the end of the procedure. Three of these were from the first six patients treated and all had gangrene of the extremity with very poor distal run off and little flow through the reopened vessel. In one case the angioplasty balloon broke and the vessel reoccluded while it was being changed, and in another the angioplasty balloon failed to deflate and had to be punctured percutaneously with a needle. In this patient the vessel reoccluded during the procedure and successful, urgent surgery was performed the following day owing to deterioration of symptoms.

Of the patients in whom successful recanalization of the superficial femoral vessel was achieved at 24 h, 20 have now been followed for a period of up to 24 months (median 7 months). Median ABPI showed an increase from 0·4 to 0·6 at rest (statistically significant: $P<0{\cdot}01$, Wilcoxon signed rank test; *Figure 3*) and from 0·2 to 0·7 following exercise. patient required a below-knee amputation for pre-existing gangrene. The stump healed well and the popliteal pulse has remained palpable. All the other patients had complete relief of symptoms. In one case there was reocclusion of the vessel 5 months after the procedure. This patient had previously suffered from rest pain and had a return of claudication at 50 m but declined further treatment. Five patients have been followed up for more than 1 year and all remain asymptomatic, with clinically patent vessels and no deterioration in ABPI (median t rest 0·8). Patency of recanalized vessels has been demonstratedat the time of angiography for symptoms of the untreated leg in two patients at 5 and 6 months after the laser procedure.

Discussion

The use of laser angioplasty, either as an adjunct to, or instead of, balloon angioplasty has two potential advantages over conventional treatment. The major advantage is that lesions that could only be treated by extensive vascular surgery may now be amenable to a relatively non-invasive form of treatment. The second possible advantage is that, because the occluding material is removed rather than simply displaced, the restenosis rate following laser treatment may be less than that seen with balloon angioplasty alone. To show this would require a prolonged randomized trial of laser *versus* conventional angioplasty, so that good evidence is unlikely to emerge for many years, although the proponents of laser thermal angioplasty are already suggesting that restenosis rates are reduced[10].

In the case of long occlusions, even when mechanical recanalization and balloon angioplasty are possible, the long term patency is poor[11]. In the early part of this trial an attempt was made to recanalize every occlusion by mechanical means before considering the use of the laser. Three occlusions of more than 15 cm were recanalized and balloon dilated, but all had reoccluded within 48 h. This trial of mechanical recanalization was therefore dropped from the protocol and only attempted if thought to be indicated by the angiographic appearance.

Because the indications for treatment and severity of disease have great bearing on the results of all forms of treatment for peripheral vascular disease[12], it is important to define the patient group accurately before comparing the results of different treatments. Laser angioplasty may be used as an alternative to balloon angioplasty for a symptomatic stenosis or short occlusion. It may also be used in lesions that are unsuitable for balloon angioplasty. Because it is less invasive than surgery it may be used in patients whose symptoms would not normally warrant intervention, or it may be an alternative to surgery in those for whom this would be the conventional choice of treatment.

In the present series the indications have been limited to this last group. The majority of patients had rest pain, ulceration or gangrene, and all had long occlusions of the superficial femoral artery which were unsuitable for balloon angioplasty. The only two patients whose occlusions were less than 5 cm in length had already undergone failed attempts at conventional balloon angioplasty. This must be taken into account when results are compared with those reported by others. For example, in the large series recently reported with the heated probe[10], two-thirds of patients were claudicants, in only a quarter was there an occlusion over 7 cm in length and over 20 per cent had a stenosis rather than an occlusion. Other groups are treating an even higher proportion of stenoses[13].

The patients who have had a successful clinical result in this series have all been saved an operation by a relatively minor procedure with few complications. Only one patient deteriorated after the procedure and this was one in whom laser recanalization was successful but the angioplasty balloon failed to deflate and the vessel reoccluded. There was no evidence that an attempt at laser angioplasty adversely affected the chances of subsequent successful surgery in any of the patients having an unsuccessful laser procedure.

Most of the unsatisfactory results were associated with problems which may well be resolved with improved devices and techniques. The major problem is failure of access, either because the device passed down a side-branch and could not be induced to go down the main channel, or because of disease or scarring in the groin. The present device is not sufficiently flexible to be passed from the brachial or contralateral femoral arteries. These problems are likely to be overcome by new devices which are at present being evaluated[9] or by using the laser in the operating theatre via a surgical exposure of the vessel. The problems relating to failure of output or sterilization of the fibre are also likely to be resolved by the development of a sterile, prepacked, disposable device. The present device is reused, mainly because of the high cost of sapphires.

Although only five patients have so far been followed up for more than a year, the initial results are promising. There has only been one late occlusion in the 20 patients followed for up to 24 months. If this trend continues then it is likely that a substantial number of patients could avoid the need for major surgery, as the life expectancy of this group of patients is known to be poor[14].

Several possible combinations of laser and device are currently under investigation for the purpose of laser angioplasty[15]. Although a sapphire device is being used elsewhere for laser angioplasty[16], this has been used with a continuous wave laser which does not have many of the theoretical advantages of direct delivery of light to the tissue. Experimental work shows that use of a pulsed laser with a transparent device can produce ablation with the minimum of surrounding damage and debris formation[9].

The current series shows that the combination of pulsed laser and transparent device is now a feasible clinical method for treatment of occlusions in the peripheral vessels and it seems likely that laser angioplasty will become a useful addition to the options for the treatment of peripheral vascular disease. If the early safety record is maintained, it may become justifiable to treat an increasing number of patients with less severe, but disabling symptoms, in whom the risks of surgery are not warranted.

Once experience has been gathered in the peripheral circulation, the extension of the technique to the coronary vessels has potential advantages over presently available methods.

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Operative assessment of femorodistal bypass grafts using a new Doppler flowmeter

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Operative measurements using a newly developed Doppler flowmeter were made on 47 in situ *femorodistal bypass grafts performed for critical ischaemia. Graft blood flow, peripheral resistance and impedance were measured before and after the injection of 15 mg papaverine down the graft. The proportion of retrograde blood flow at the distal anastomosis was also measured. The success of a graft at 1 month was defined by patency on duplex ultrasound scanning, a rise in the Doppler ankle pressures and an improvement in the clinical state of the limb. By these criteria the 1-month primary success rate was 35 out of 47 (74 per cent). Graft blood flow was of little value in predicting graft outcome but, combined with segmental pressures, accurately located six of eight technical problems which were successfully corrected. After papaverine, the peripheral resistance of all the successful grafts fell below one peripheral resistance unit (PRU). No single measurement was able to completely distinguish between success and failure, although discriminant analysis of all measurements was able to predict success with a sensitivity of 100 per cent and specificity of 97 per cent. A simpler combination of a peripheral resistance after papaverine <1 PRU and a retrograde blood flow <33 per cent predicted success, with a sensitivity of 97 per cent and specificity 83 per cent. These criteria have been validated on a further 26 grafts, achieving a sensitivity of 88 per cent and a specificity of 75 per cent. Simple operative measurements, using a newly developed Doppler flowmeter, enable the detection of technical problems and the accurate prediction of the early outcome of femorodistal grafting.*

Keywords: Doppler ultrasound, blood flow, femorodistal bypass

Despite recent advances, such as the *in situ* technique, up to one-third of all femorodistal bypass grafts performed for critical ischaemia occlude within the first year, the majority within the first month[1]. A retrospective study of 85 *in situ* vein grafts performed at the Bristol Royal Infirmary found that the 1-month occlusion rate was 20 per cent, despite the peroperative use of a pulse volume recorder[2]. Early failure may lead to a higher level of amputation[3], a lengthy hospital stay and wasted operating time.

It has been known for over 20 years that graft patency is dependent on blood flow[4] but many vascular surgeons are still hampered by a lack of haemodynamic information during reconstruction. Electromagnetic flowmeters are expensive and can be difficult to use in theatre[5], and completion arteriography provides little information about the functional capacity of the run off[6]. Indirect methods such as Doppler ankle pressures[7], plethysmography[8] and transcutaneous oxygen tension[9] are generally easy to use and relatively inexpensive. However, there may be a significant delay before a positive result is recorded in a successful graft and a negative result does not indicate the cause of the problem.

The object of this study was to evaluate the use of a newly developed Doppler flowmeter[10] during femorodistal reconstruction to detect technical problems and to see whether the early outcome could be predicted.

Patients and methods

Forty-seven consecutive *in situ* vein femorodistal bypass grafts performed for critical ischaemia[11] were studied prospectively. There were 25 men and 18 women aged between 42 and 87 years (median 71 years); four patients received bilateral grafts. Thirty-three operations were performed for tissue loss, the other 14 for persistent rest pain; 12 patients were diabetic. Preoperative assessment was based on a combination of clinical examination, transfemoral arteriography and Doppler ankle pressures.

The 'non-reversed' technique of *in situ* vein bypass was used in all cases[2]. The vein was completely exposed and mobilized to avoid the risk of arteriovenous fistulae. Valve disruption was performed from the distal end using a Hall valvulotome once the vein was distended with blood from the completed proximal anastomosis[12]. The proximal anastomosis was to the common femoral artery in 44 cases and to the lower end of a previous aortofemoral graft in three. The distal anastomosis was to the popliteal artery below the knee in 28 cases, the tibioperoneal trunk in ten and a single calf vessel in nine. Five preoperative transluminal angioplasties and three endarterectomies were performed to improve the iliac artery inflow.

The Doppler flowmeter is based on a 10 MHz pencil probe and a mean frequency estimator whose output is proportional to the mean blood velocity[10]. The errors associated with measurement of the vessel diameter and angle of insonation[13] are minimized by clipping a plastic cuff snugly around the vessel which fixes the probe angle at 50°. A range of cuffs from 3 to 14 mm have been constructed, as well as a compression gauge which is used to measure the vessel wall thickness and hence the vessel internal diameter (*Figure 1*). The probe, cuffs and gauge are all sterilized by activated glutaraldehyde. Blood flow is calculated by the flowmeter from the mean blood velocity and the vessel internal diameter using an experimentally determined calibration factor to compensate for uneven insonation of the vessel lumen. Unlike electromagnetic instruments, the Doppler flowmeter is easy to use because no zeroing is required and, provided a signal is obtainable, its sensitivity is unaffected by the vessel wall composition. Because it does not depend on electrical contact with the vessel, flow can be measured in non-conductive materials including thin-walled polyvinylchloride shunts and polytetrafluoroethylene grafts, provided that they are wetted well to remove any air bubbles in the wall.

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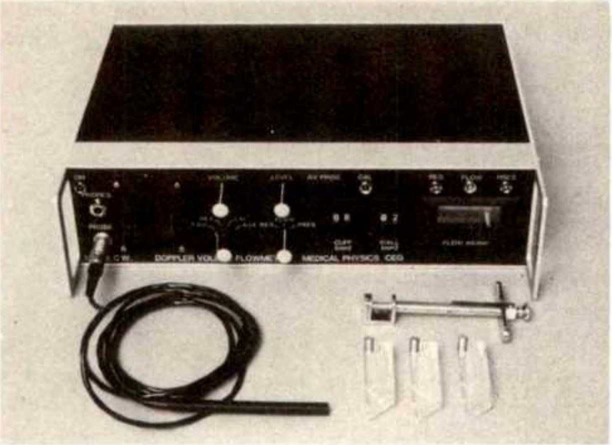

Figure 1 *The Doppler flowmeter together with the 10 MHz pencil probe, a range of acrylic cuffs and the compression gauge*

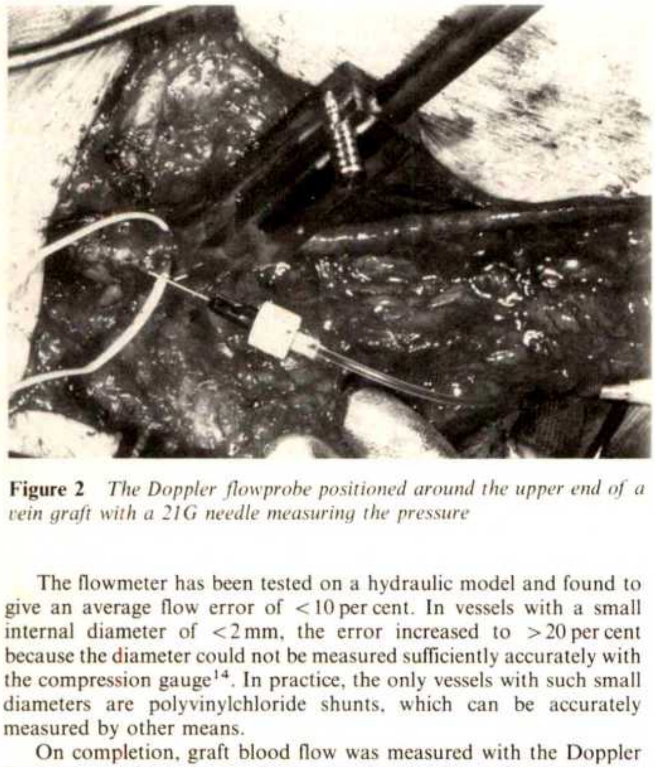

Figure 2 *The Doppler flowprobe positioned around the upper end of a vein graft with a 21G needle measuring the pressure*

The flowmeter has been tested on a hydraulic model and found to give an average flow error of <10 per cent. In vessels with a small internal diameter of <2 mm, the error increased to >20 per cent because the diameter could not be measured sufficiently accurately with the compression gauge[14]. In practice, the only vessels with such small diameters are polyvinylchloride shunts, which can be accurately measured by other means.

On completion, graft blood flow was measured with the Doppler flowprobe positioned near the proximal end. The graft pressure was also measured with a Gould P231D® (Gould Incorporated, Oxnard, California, USA) pressure transducer connected to a 10-cm length of manometer tubing and a 21G (green) needle inserted into the graft (*Figure 2*). After measuring the total graft flow, the popliteal artery proximal to the distal anastomosis was occluded to prevent retrograde flow and the distal flow was measured. The amount of retrograde flow was then expressed as a percentage of the total, where

$$\text{Retrograde flow} = \frac{\text{Total flow} - \text{Distal flow}}{\text{Total flow}}$$

The peripheral resistance was then calculated from the mean distal graft blood pressure and flow and expressed in peripheral resistance units (PRU), where 1 PRU = 1 mmHg ml^{-1} min^{-1}. The mean systemic blood pressure was also recorded from a cannula inserted into the radial artery. This allowed calculation of the proximal inflow resistance of the iliac artery, where

$$\text{Proximal resistance} = \frac{\text{Systemic pressure} - \text{Graft pressure}}{\text{Graft flow}}$$

The peripheral resistance was then measured again after the injection of 15 mg papaverine down the graft. The peripheral resistance was measured when graft flow was maximal, which was usually within 1 min; flow returned to baseline within 3 min. If the peripheral resistance failed to fall after papaverine then the pressures at the distal end of the graft and in the artery below the anastomosis were measured. If there was a pressure drop >10 mmHg, a valvulotome was repassed to exclude persistent valve cusps, or the distal anastomosis was revised. An arteriogram was obtained if the problem was more distal and an embolectomy was performed if indicated.

During measurement of the peripheral resistance, the pressure and flow waveforms were also stored digitally on an Apple 2E® (Apple Computer Company, Cupertino, California, USA) microcomputer. The input impedance curve was subsequently calculated by Fourier transformation analysis and the area under the curve up to 40 rad was measured. Measurement of the input impedance is theoretically superior to resistance as it also looks at the frequency dependent elements of the arterial system[15].

The success of a graft at 1 month was defined by patency on duplex ultrasound scanning, a rise in the postoperative Doppler ankle: brachial pressure index of >0·25[16] and a clinical improvement in the limb. Statistical analysis was by the Mann–Whitney *U* test with analysis of variance for each parameter and by discriminant analysis of all the parameters combined.

Results

According to the above criteria, 35 grafts were successful at 1 month (primary success rate 74 per cent). Of the 12 failed grafts, eight occluded between 12 h and 19 days postoperatively, and four grafts, although patent, resulted in no improvement clinically or in the Doppler ankle pressures. Of the 12 failures, eight were revised, four successfully.

The results of all the measurements are summarized in *Table 1*. Although there was a significant difference between the total blood flow of successful and failed grafts ($P = 0·02$), it was of little value in predicting graft outcome. Measurement of flow combined with segmental pressures accurately located six of eight technical problems, which were successfully corrected. These included two persistent valve cusps, one anastomotic stenosis, one kinked graft and two distal thromboemboli. The two missed problems were a graft that kinked on extension of the knee following skin closure and an intimal dissection at a distal anastomosis. Both caused occlusion within 24 h but these were two of the grafts that were successfully revised. The other two successful revisions received distal extensions to bypass disease at the origins of the tibial vessels.

There was a statistically significant difference in the graft flow distally between the successful and failed grafts ($P = 0·002$) although there was still a considerable overlap between success and failure, one successful graft having a flow of only 24 ml min^{-1}. The proportion of retrograde flow at the distal anastomosis was not significantly different by itself ($P = 0·18$), although the proportion in five failed grafts was >33 per cent. The proximal resistance of the iliac artery was also not significantly different in successful and failed grafts ($P = 0·13$). Although two failures had high resistances of around 0·4 PRU, they both had other potential reasons for failure.

The peripheral resistance before papaverine was of similar significance to the distal flow (*Figure 3a*; $P = 0·002$) but was

Table 1 *Results of measurements on 47 femorodistal* in situ *vein grafts*

Measurement	Success	Failure	*P*
Proximal resistance (PRU)	0·05 (0–0·27)	0·08 (0–0·43)	0·13
Total flow (ml min^{-1})	96 (34–196)	61 (15–123)	0·02
Distal flow (ml min^{-1})	81 (24–184)	42(14–115)	0·002
Retrograde flow (ml min^{-1})	15 (−4–41)	19 (−8–46)	0·18
Resistance (PRU)			
Before papaverine	1·15 (0·41–2·61)	1·99 (0·45–3·12)	0·002
After papaverine	0·51 (0·26–0·88)	1·16 (0·27–2·08)	0·0001
Impedance			
Before papaverine	45 (21–66)	41 (13–58)	0·15
After papaverine	68 (32–91)	51 (18–70)	0·004

Values are median (range). PRU, peripheral resistance unit. Statistical analysis was by the Mann–Whitney *U* test

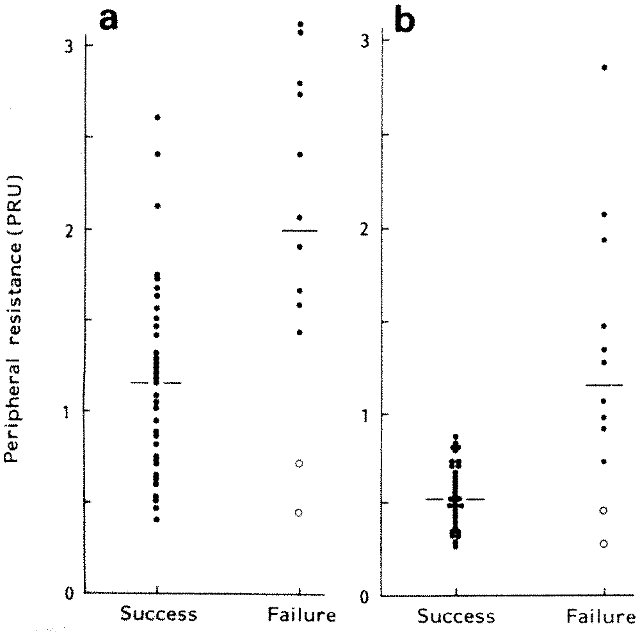

Figure 3 *Peripheral resistance for successful and failed grafts* **a** *before papaverine* (P = 0·002) *and* **b** *after papaverine* (P = 0·0001). *PRU, peripheral resistance units;* ○, *missed technical problem; statistical analysis was by the Mann–Whitney* U *test*

highly significantly different in successful and failed grafts after papaverine (*Figure 3b*; $P = 0{\cdot}0001$). After papaverine the peripheral resistance of all the successful grafts fell below 1 PRU, whereas the failures tended to remain high. Four failed grafts with borderline peripheral resistances had a retrograde flow >33 per cent. These were the four grafts that, although patent at 1 month, resulted in no clinical or Doppler improvement. Arteriograms were obtained for all grafts with a poor response to papaverine once a more proximal technical problem had been excluded. These all showed severe distal disease except for the two cases where thromboemboli were successfully removed.

The input impedance before papaverine was not significantly different ($P = 0{\cdot}15$) but this was not the case after papaverine ($P = 0{\cdot}004$). Following papaverine the impedance curves of the successful grafts flattened out, becoming predominantly resistive.

Although no single measurement was able to completely distinguish between success and failure, discriminant analysis of all parameters achieved a correct classification of all of the 35 successes and 11 of the 12 failures (sensitivity 100 per cent, specificity 97 per cent). A much simpler combination of peripheral resistance after papaverine <1 PRU and a retrograde flow <33 per cent achieved a sensitivity of 97 per cent and a specificity of 83 per cent. The only failures not correctly classified were the two missed technical problems.

These criteria have now been validated on a further series of 26 consecutive femorodistal grafts. Four technical problems were detected and corrected. Successful graft outcome at 1 month was predicted in 16 of 18 cases, with a sensitivity of 88 per cent and a specificity of 75 per cent. This series included four very distal grafts to tibial vessels near the ankle. These tended to have a lesser response to papaverine and a higher proportion of retrograde flow without compromising distal perfusion.

Discussion

The Doppler flowmeter is now used routinely during all types of arterial reconstructive surgery, including femorofemoral and femorodistal bypass and carotid endarterectomy. It has proved easy to use in the operating theatre without technical support. No electrical contact with the vessel or zeroing is required and there is no change in sensitivity with different graft materials. Although initial calibration of the system is required, regular calibration of individual probes is unnecessary. The need for only one transducer also reduces costs.

It should be no surprise that measurement of resistance was better than that of flow alone. Graft blood flow is dependent on many factors, apart from the run off, including the systemic blood pressure and the tone of the capillary bed, both of which may also be dependent on the anaesthetic[17]. Measurement of the peripheral resistance avoids errors due to poor graft perfusion and the administration of papaverine reduces errors due to variable capillary tone[18]. Graft blood flow in the early postoperative period increases as the capillary bed opens up[19] and this may explain why measurement of resting flow or peripheral resistance before papaverine are less good at predicting outcome.

Interestingly, a resting blood flow of 120 ml min^{-1} was recorded in a vein graft with a minimum diameter of only 2 mm. This suggests that, even for small calibre grafts, blood flow is limited more by the peripheral resistance than by the diameter. Although both the grafts with a high proximal iliac resistance had other potential reasons for failure, it seems likely that it was a contributing factor. Although more moderate iliac disease may not cause femorodistal graft failure[20], it may limit its maximum potential. Correction by transluminal angioplasty, endarterectomy or grafting seems advisable if full clinical benefit is to be obtained.

A high retrograde flow of blood at the distal anastomosis was usually found in combination with a high peripheral resistance due to distal disease, resulting in retrograde flow up a patent proximal popliteal artery. This situation is analogous to the formation of an arteriovenous fistula at the distal anastomosis, or leaving a venous tributary intact. Blood may be shunted away from the distal circulation even though graft patency is maintained[21]. All four grafts that remained patent without any clinical or Doppler improvement had retrograde flows >33 per cent. A high retrograde flow suggests that the distal anastomosis may require revision to a more distal level. For very distal grafts near the ankle, a high retrograde flow may not impair distal perfusion and probably helps to maintain patency. These grafts also have a lesser response to papaverine, perhaps because of the smaller volume of muscle perfused.

The use of input impedance to predict graft function was disappointing, despite its theoretical advantages. Most of the differences between success and failure were in the resistive elements which were more simply assessed by measurement of the peripheral resistance.

In conclusion, simple operative measurements during femorodistal bypass, using a newly developed Doppler flowmeter, enable most technical problems to be detected and early graft outcome to be accurately predicted. This should lower the incidence of early graft failure, with a consequent reduction in patient morbidity, hospital stay and wasted operating time.

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Surgical workshop

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Saphenous vein in infrainguinal bypass

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It is generally accepted that autogenous saphenous vein is the best graft material for bypass procedures below the inguinal ligament. When a satisfactory single length of saphenous vein is not available for reversed, *in situ* or non-reversed translocated techniques, totally autogenous composite grafts consisting of different combinations of greater and lesser saphenous vein and/or arm veins have been advocated to obtain an adequate length to revascularize ischaemic limbs[1,2]. More recently a new graft has been reported using arm veins to give a combination of reversed cephalic and non-reversed basilic vein in continuity that is long enough for distal reconstructions[3].

We have used an analogous technique in two patients with double greater saphenous vein trunks, each of which had insufficient length on its own to complete a femoropopliteal below-knee bypass. Both branches of the saphenous vein were mobilized for as far as their diameters were adequate. The trunk with the larger diameter was reversed and used as the proximal part of the graft, the distal part consisting of the smaller non-reversed trunk. The valves in the non-reversed segment were destroyed with a valvulotome introduced from the distal end of the graft. The excised bifurcation area was sutured (*Figure 1*).

This technique avoids the need for an additional venovenous anastomosis to obtain the requisite graft length in cases with a double greater saphenous vein where each trunk is not on its own long enough to complete the bypass procedure.

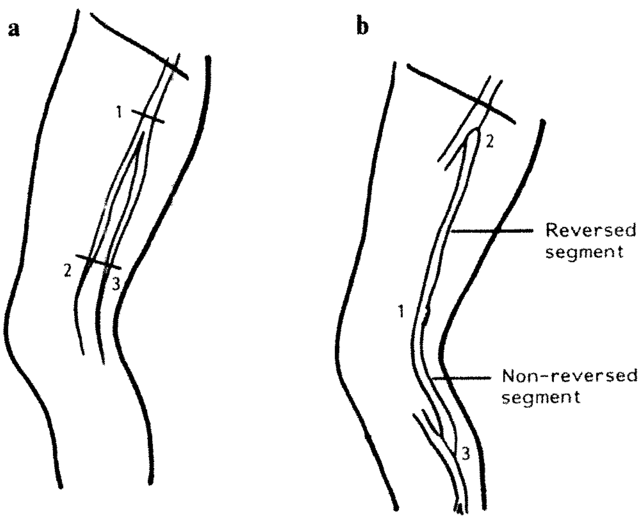

Figure 1 *Diagrams showing the orientation of the double saphenous vein* **a** *before and* **b** *after completion of bypass procedure*

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Evaluation of non-invasive and invasive methods in the assessment of short saphenous vein termination

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Surgery of the short saphenous vein is associated with a high recurrence rate because of variations in the anatomy or inadequate clinical examination. To prevent this, accurate definition of the pattern and level of termination of the saphenopopliteal junction and flush ligation is necessary. Clinical examination, Doppler ultrasound, duplex scanning and peroperative venography have been compared to assess the level of termination of the short saphenous vein. In all, 64 limbs of 46 patients were examined. In 39 limbs there was primary short saphenous incompetence, in 13 limbs there was recurrent short saphenous incompetence; in ten of these there was incompetence of the gastrocnemius vein. In 12 limbs a duplex scan did not demonstrate incompetence of the short saphenous vein or gastrocnemius vein. The accuracy of these methods when locating incompetence of the short saphenous vein to within 2 cm of the saphenopopliteal junction was 56 per cent for clinical examination, 64 per cent for Doppler ultrasound and 96 per cent for duplex scanning. When there was no saphenopopliteal junction (9 per cent), duplex scanning correctly detected the pattern of the incompetent vein. The apparent success of clinical examination was because the vein was not felt above the femoral intercondylar groove and 52 per cent of the veins terminated at this level. Duplex scanning is a non-invasive technique which is almost as accurate as venography and provides additional haemodynamic information about the incompetent veins by demonstrating the presence and extent of reflux.

Keywords: Short saphenous vein, Doppler ultrasound, duplex scanning, peroperative venography

Surgery of the short saphenous vein is a common surgical procedure, associated with a high recurrence rate[1]. This is due to variations of the anatomy which are not always detected before operation, with the result that flush saphenopopliteal ligation is not always achieved.

The usual methods of assessing the short saphenous system are clinical examination and the use of Doppler ultrasound. These, together with venography[2–4], which remains the gold standard, are able to demonstrate the presence of reflux and detect the level of the saphenopopliteal junction.

Recently, duplex scanning was introduced[5] in the study of venous disease with promising results. It has been shown to be very accurate in the detection of venous thrombosis[6,7] and deep vein insufficiency[8].

The aim of this study was to compare clinical examination, Doppler ultrasound and duplex scanning with peroperative venography for the detection of the level and pattern of termination of the short saphenous vein.

Patients and methods

The short saphenous vein termination was examined in the vascular laboratory before operation in 46 patients (64 limbs). There were 17 men (mean age 45·2 years) and 29 women (mean age 47·9 years). Primary short saphenous vein insufficiency was found in 39 limbs (61 per cent) and recurrent insufficiency in 13 (20 per cent). In 12 limbs the short saphenous vein was found to be competent but these were included in the study because, although the distal short saphenous vein was involved, there was incompetence due either to a communication from the long saphenous vein or to the midcalf perforating vein. In these cases only duplex scanning could be compared with venography.

Clinical examination was performed with the patient standing and the knee flexed so that the fascia over the popliteal fossa was relaxed. The short saphenous vein was palpated and followed proximally until it could no longer be felt. This was assumed to be the level of its junction with the deep system and was marked on the skin.

Doppler ultrasound examination was then performed. A pocket CW directional Doppler flowmeter with an 8 MHz probe was used (Sonicaid® BV102, Oxford Sonicaid Ltd., Chichester, UK). The patient was standing, facing away from the examiner and holding on to a frame or table. The knee on the side to be examined was flexed so that the popliteal fascia was relaxed. The Doppler probe was positioned on the skin over the popliteal fossa at an angle of approximately 45° so that the signals from the popliteal artery and popliteal vein were audible. The calf was then manually compressed and venous flow towards the heart was detected. On release of compression, if insufficiency was present, a retrograde venous flow was detected. This indicated reflux into either the short saphenous vein or the popliteal vein. When reflux was heard the calf compression was repeated but now with compression of the short saphenous vein by an assistant distal to the probe. If reflux persisted despite digital compression of the short saphenous vein, it was inferred that the reflux is located in the popliteal vein. If abolished, the reflux was considered to be in the short saphenous vein[9]. After the reflux in a proximal direction, the site of termination of the short saphenous was determined to be the highest level of the detection of reflux. This level was marked on the skin.

Duplex examination was performed using a 7·5 or 10 MHz imaging crystal coupled with a 3·0 MHz pulsed Doppler crystal (Diasonics® DRF300, Diasonics–Sonotron, Bedford, UK). The patient was examined as for the Doppler study. The probe was positioned over the skin of the popliteal fossa longitudinally and adjusted so that three structures were identified: the pulsating popliteal artery lying deepest, the popliteal vein lying more superficial and parallel to it and, even more superficial, the short saphenous vein (*Figure 1*). Because of anatomical variations, careful scanning was performed above and below the popliteal fossa to identify all the vascular structures. The gastrocnemius veins were easily recognized by their deep course between the popliteal vein and short saphenous vein and by their emergence from the gastrocnemius muscle. They often communicated distally with the midcalf perforating vein. Another common vein of the area was the Giacomini vein

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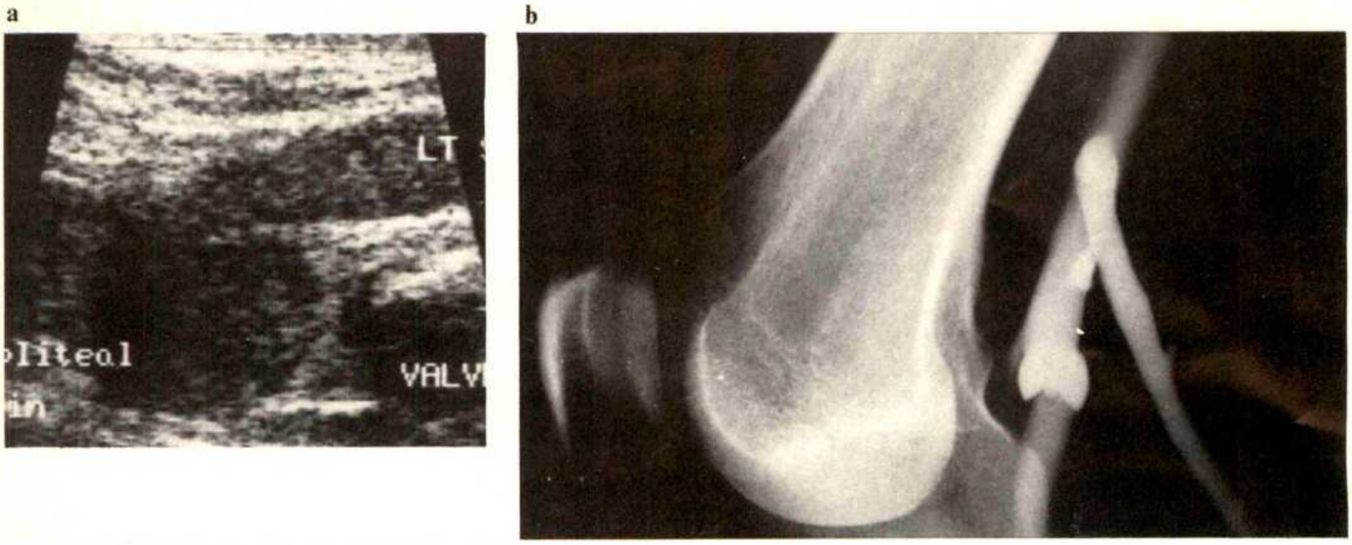

Figure 1 **a** *Duplex imaging of the popliteal fossa. The short saphenous vein, popliteal vein and the saphenopopliteal junction are demonstrated. A valve is shown in the popliteal vein.* **b** *The peroperative venogram of the same patient showing the level of termination and the valve in the popliteal vein, confirming the duplex findings*

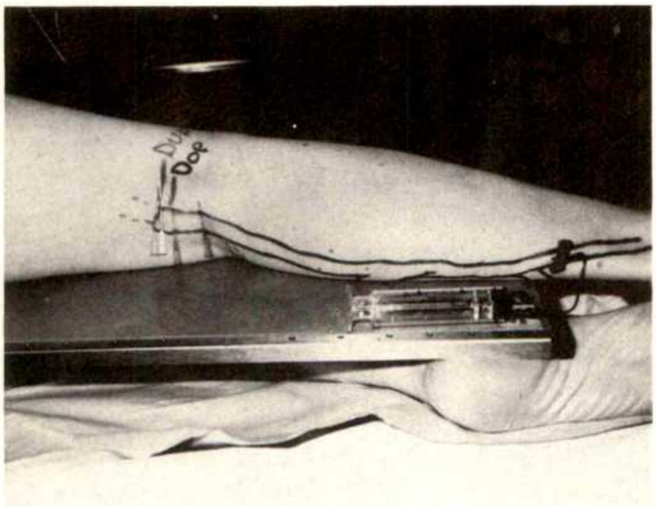

Figure 2 *Method of peroperative venography. The needles are used as markers for the level of termination of the short saphenous vein*

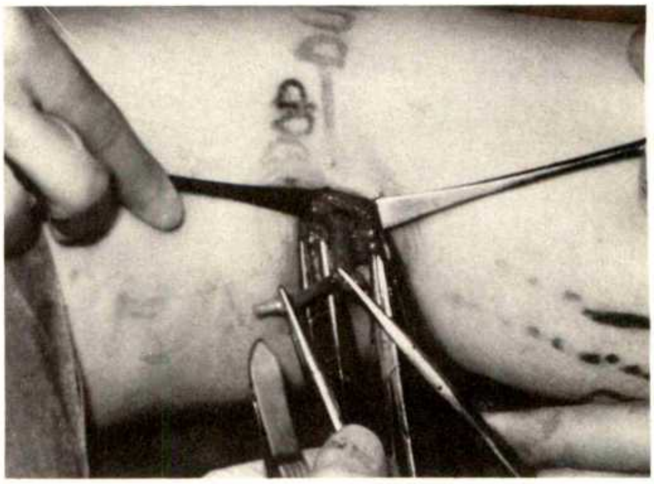

Figure 3 *The saphenopopliteal junction exposed through a small incision. Note the accuracy of duplex scanning in detecting the level*

(femoropopliteal vein) that ascends from the proximal part of the short saphenous vein deep in the posterior aspect of the thigh, parallel to the skin, to terminate as the posteromedial tributary of the long saphenous vein or rarely by joining tributaries of the internal iliac veins. The flow in these veins was assessed by focusing the pulsed Doppler scanner in the lumen and manually compressing the calf. On sudden release, if there was incompetence, retrograde flow was detected and the grey scale spectrum was recorded. Thus, all incompetent sites were recorded. By following the course of the incompetent vein proximally using continuous imaging, the level of the junction with the deep system was detected and marked on the skin. If more than one vein was incompetent, e.g. the short saphenous and gastrocnemius veins, each site was marked.

At operation the patient was placed in a lateral position and a peroperative venogram, previously described[10], was performed. Hexabrix® (May and Baker Ltd., Dagenham, UK) or Niopam® 300 (E. Merck Ltd., Alton, UK) was used as the contrast and usually 20 ml were enough to visualize the anatomy. Needles of different sizes were placed at the sites of skin marked and used as markers for comparison on the venogram (*Figure 2*). After on-table venography the operation was performed with the patient in the lateral position using a small skin incision. The operative findings confirmed the accuracy of the various techniques (*Figure 3*).

Results

The level of the saphenopopliteal junction is shown in *Figure 4*. In 56 per cent the termination was within 2–5 cm of the knee joint. This was also the level of the femoral condyle and usually the short saphenous vein could not be palpated above this level, giving the impression that the clinical assessment was accurate. In 27 per cent the short saphenous vein terminated more than 5 cm above the knee joint and in six cases (9 per cent) joined the long saphenous vein. In one leg the proximal part of the short saphenous vein was absent, the distal part connecting to the gastrocnemius vein via a midcalf perforator. In this limb the termination of the gastrocnemius vein was determined and found to be 1 cm above the knee joint. Duplex scanning detected the presence of an incompetent gastrocnemius vein in ten legs (16 per cent), of which seven were in association with primary short saphenous insufficiency and three were the cause of recurrence after previous short saphenous ligation and stripping. There were also five examples of saphenopopliteal incompetence via the Giacomini vein detected by duplex scanning. In all legs venography accurately (100 per cent) located the level of the junction as confirmed by the intraoperative findings.

The results of each method are presented as percentages measured to detect the level of the junction in *Table 1*. We accept the distance of ±2 cm from the junction as the maximum distance needed to perform an accurate flush ligation. Venography always demonstrates the junction, while duplex scans have an accuracy of 96 per cent, compared with 56 per cent by clinical examination and 64 per cent by Doppler. In 9 per cent

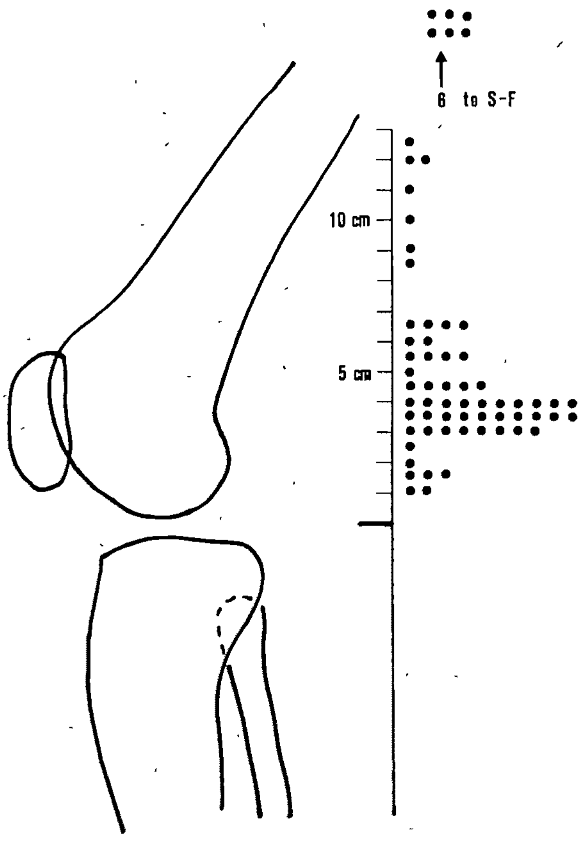

Figure 4 *Level of termination of the short saphenous vein as shown by venography (centimetres above knee joint). In six cases the short saphenous vein joined the long saphenous vein (S-F), in one leg the short saphenous vein (SSV) was absent*

of legs where there was no junction, duplex examination correctly visualized the anatomy.

The 100 per cent accuracy of venography was achieved with only one film in the majority of examinations. In nine limbs a second and in three limbs a third film was required to demonstrate the termination pattern. In the limbs in which duplex was unable accurately to locate the junction it was because the vein continued deep in the thigh or there was an anterior termination of the short saphenous vein in the popliteal vein, resulting in poor image resolution. The average time of examination needed for duplex scanning was 5 min.

Table 1 *Accuracy of the four techniques in detecting the level of termination of the short saphenous vein*

	Accuracy (%)		
	At the junction	At ±1 cm	At ±2 cm
X-ray	100	100	100
Clinical	9	31	56
Doppler	8	21	64
Duplex	29	50	96*

Data are measured from the level of the junction. In 9 per cent of limbs where no junction was present duplex examination correctly demonstrated the anatomy, and the overall accuracy of the technique was 96 per cent. * This figure includes the six limbs in which the duplex scan indicated that the short saphenous vein was not connected to the popliteal vein

Discussion

The level of termination of the short saphenous vein is variable[2,3,10–15]. In the majority (60 per cent) there is a distinct saphenopopliteal junction 2–7 cm above the level of the knee joint. In 30 per cent the short saphenous vein joins the deep system in the thigh or continues to the proximal long saphenous vein. In 10 per cent there is a low termination in the calf joining the gastrocnemius vein via the midcalf perforator or the long saphenous vein via a communicating vein. In our series 26 per cent of limbs showed a high termination of the short saphenous vein, which corresponds with previous reports.

Clinical examination appeared to be accurate but was not confirmed by this study. Clinical examination can easily detect a dilated short saphenous vein but provides uncertain information about the termination level or pattern.

Doppler ultrasound was not found to be as accurate as previously claimed[16]. It demonstrated the highest level where reflux was detected, which was not always the level of the saphenopopliteal junction. It could not differentiate between reflux in the popliteal vein and in the gastrocnemius or Giacomini veins. This may explain the 5 per cent error found when Doppler alone was used for the detection of popliteal reflux[9]. Doppler examination can accurately detect the presence of reflux in the area[17] but, in our experience, it did not always locate the level and pattern of the saphenopopliteal junction.

Peroperative venography provided 100 per cent accuracy on the level and pattern of termination of the short saphenous vein. If there was any doubt the venogram was immediately repeated, sometimes using a different injection site. However, although providing accurate anatomical information, this method did not demonstrate the presence and site of reflux.

Duplex scanning, a non-invasive technique, is almost as accurate in determining the level of the saphenopopliteal junction as venography It can also demonstrate the presence of reflux in individual veins. It is possible for the first time using a non-invasive technique to demonstrate the presence of reflux at the short saphenous vein termination. Duplex scanning can also diagnose and demonstrate incompetence of the gastrocnemius vein[18]. The few cases in which duplex scanning was not accurate were a result of unusual anatomy and of the resolution of the machine. In the near future, with new-generation machines, the higher imaging resolution and penetration may achieve an almost 100 per cent accuracy for duplex scanning. The technique has the advantage that it is non-invasive, takes about 5 min, and is easily repeated. The disadvantage is that such machines are not available in every district hospital and experience is required for its use. When it is not available, venography remains a reliable method of visualizing the anatomy of the veins in the popliteal fossa.

It is concluded that duplex scanning, when available for arterial studies, should also be used for the assessment of the short saphenous vein. This, in combination with venography, will reduce the high recurrence rate seen after short saphenous vein surgery by obtaining accurate assessment of the anatomical and haemodynamic variations in the area.

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Randomized study of adjusted versus fixed low dose heparin prophylaxis of deep vein thrombosis in hip surgery

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A randomized study of adjusted versus *fixed low dose heparin prophylaxis has been conducted in 100 patients undergoing surgery for hip replacement or fractured neck of femur. The two types of patients were randomized independently into the adjusted and fixed dose regimens. Patients in the adjusted group were controlled by an activated partial thromboplastin time method particularly responsive to the anticoagulant effect of heparin. The aim was to maintain the peak value just above the upper limit of the normal range. Adjustment of dosage began 24 h after surgery in the replacement group and 24 h after admission in the fracture group. Significant improvement in protection against postoperative deep vein thrombosis, assessed by venography, was observed in the adjusted group undergoing hip replacement* ($P=0.013$) *and overall in both groups* ($P=0.017$) *compared with a conventional fixed dose subcutaneous regimen (calcium heparin 5000 units, 8-hourly). In most instances, adjustment resulted in increased heparin dosage but this was not associated with any evidence of excessive bleeding.*

Keywords: Heparin, deep vein thrombosis, hip surgery

Subcutaneous heparin in fixed low dosage is of limited value in preventing venous thromboembolism in patients undergoing hip surgery[1]. We have previously shown that the anticoagulant effect, whether measured by activated partial thromboplastin time or anti-Xa assay, is variable when this regimen is given to patients undergoing major surgery[2]. Dose adjustment according to clotting response was considered in a further study of the prevention of venous thrombosis. Patients on heparin in whom prophylaxis failed after hip surgery were found to give activated partial thromboplastin times less than the upper limit of normal[3]. Levraz *et al.* subsequently reported that heparin dose adjusted according to the activated partial thromboplastin time response provided better protection after total hip replacement[4], but in their study the adjusted dose group was contrasted with a conservative fixed dose regimen (3500 units 8-hourly). In the present investigation, adjusted dosage of calcium heparin is contrasted with a conventional fixed dose (5000 units 8-hourly) in patients undergoing elective hip replacement or surgery for fractured femur.

Patients and methods

One hundred patients requiring operative treatment of total hip replacement or fractured neck of femur over a 2-year period from July 1985 were admitted to the study after giving informed consent. Exclusions comprised patients with any underlying bleeding tendency, hepatic disease, uncontrolled hypertension, active peptic ulceration, previous history of thromboembolism, cerebrovascular accident, oral anticoagulant treatment, aspirin ingestion during the previous week, allergy to iodide, pathological fracture and malignant disease. Patients were allocated to the adjusted dose regimen or the fixed dose heparin group according to random tables. Those with fractures and undergoing hip replacements were randomized independently

Hip fractures

Heparin (Calciparine®, Sanofi UK, Manchester, UK) 5000 units was administered subcutaneously 8-hourly after admission In the fixed dose regimen, this was continued until the 14th postoperative day if the patient was mobile or until the day of complete mobilization. Patients with hip fractures in the adjusted dose group received 5000 units 8-hourly for the first 24 h. Heparin was then adjusted daily according to the activated partial thromboplastin time result. The target range was 50–55 s. The adjusted dose heparin was injected by calibrated syringes, allowing the dose to be varied by 1250 units.

Hip replacements

Patients were given their first dose of 5000 units heparin with the premedication and subsequently treated with a fixed dose or with adjustment as above

Blood samples for measurements of the activated partial thromboplastin time

Blood was collected daily, 3 h after the morning dose of heparin, using a 19 gauge butterfly needle (discarding the first 2 ml) The specimen was immediately placed in 3·13 per cent trisodium citrate ($Na_3C_6H_5O_7$ $2H_2O$) in plastic containers (nine volumes of blood to one volume of anticoagulant) and kept at 4°C It was transported without delay to the laboratory and processed as previously described, using the Manchester activated partial thromboplastin time reagent[3]

Diagnosis of deep vein thrombosis

[^{125}I]-labelled fibrinogen scanning was performed as previously described[3]. Ultrasound examination of femoral vein flow was undertaken using a Sonicaid BV102® blood flow detector (Sonicaid Ltd, Chichester, UK). These tests were performed daily, excluding Saturdays and Sundays. Impedence plethysmography was carried out at the end of the first and second postoperative weeks Venography was performed to confirm the presence of venous thrombosis if any of the above screening tests were positive

Blood loss

Postoperative blood drainage was measured. The amount of blood transfused and haemoglobin levels were recorded before operation and during the first and second postoperative weeks.

Wound haematoma

A clinical evaluation of wound sites for haematoma was made daily

Comparability of patient groups

The distribution of age, weight, sex and type of surgery was analysed for the two treatment groups

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Table 1 *Comparability of groups*

Parameter	Fracture group Adjusted dose (*n*=14)	Fracture group Fixed dose (*n*=14)	Replacement group Adjusted dose (*n*=40)	Replacement group Fixed dose (*n*=32)
Mean age (years)	73·8 (43–91)	78·7 (56–90)	64·8 (26–80)	66·0 (0–84)
Male patients (%)	8	21	35	43
Patients with rheumatoid arthritis (%)	7	0	7	3
Mean weight* (for height, %)	92·3 (80–114)	88·2 (63–114)	102·0 (80–131)	97·5 (82–143)

Values in parentheses are ranges. * Mean weight is expressed as a percentage for height

Table 2 *Results of screening tests for deep vein thrombosis and venograms*

Parameter	Fracture group Fixed dose (*n*=14)	Fracture group Adjusted dose (*n*=14)	Replacement group Fixed dose (*n*=32)	Replacement group Adjusted dose (*n*=40)
Positive screening tests				
Fibrinogen scan	5	4	12	10
Plethysmography	1	0	3	3
Ultrasound	1	1	3	0
Negative screening tests	8	10	18	27
Withdrawals	1	1	2	2
Venograms				
Positive				
Proximal	1	0	1	0
Distal	1	1	5	0
Negative	1	1	3	6
Unsatisfactory	1	0	2	2
Patient unfit	0	2	1	3
Incidence of venographically proved deep vein thrombosis	2 (14)	1 (7)	6 (19)	0

Values in parentheses are percentages

Table 3 *Incidence of deep vein thrombosis*

	Incidence Fixed dose	Incidence Adjusted dose	*P*
Replacements	19 (8·6–35·7)	0 (0–8·6)	0·013
All patients	17 (8·2–32·0)	2 (0–10·6)	0·017

Values are percentages with confidence intervals in parentheses. Statistical analysis was by Fisher's exact test

Results

There were 72 patients in the elective hip replacement group, one of whom did not proceed to surgery. These were well matched according to the comparability criteria. There were 28 patients with fractures but these showed minor differences between the fixed dose and adjusted dose groups (*Table 1*).

The presence of deep vein thrombosis was confirmed by venography in nine patients. Eight were in the fixed dose group and one in the adjusted dose group (*Table 2*). The incidence was 2 per cent in the adjusted dose group and 17 per cent in the fixed dose group. This difference was significant ($P=0{\cdot}017$, Fisher's exact test; *Table 3*). When the hip replacements were analysed separately, the incidence of venous thrombosis was lower in the adjusted regimen compared with the fixed regimen ($P=0{\cdot}013$). No positive venograms were found in the adjusted group, compared with six in the fixed dose patients. The numbers of patients with fractures was too small for separate analysis.

Venograms were obtained in 20 of the 31 patients with positive screening tests. In the remaining 11 patients a satisfactory venogram was not obtained. The patients were equally distributed between adjusted and fixed groups (11 per cent in each).

During the postoperative phase before the occurrence of deep vein thrombosis, the activated partial thromboplastin time was less than 50 s, the lower limit of the target range, in five of the six hip replacement patients who developed venographically proved thrombosis. The sixth patient had a satisfactory prolonged clotting test before diagnosis of thrombosis, at which time the test had become accelerated. The six patients were all in the fixed dose group as there were no failures of prophylaxis in the adjusted group with elective replacements.

In the hip fractures, prophylaxis failed in one adjusted dose patient. The activated partial thromboplastin time remained below the lower limit of the normal range and well below the target value in spite of considerable increase of dosage to 11 250 units every 8 h. A therapeutic effect was only observed after confirmation of the deep vein thrombosis. In two hip fracture patients receiving fixed dosage prophylaxis failed. The activated partial thromboplastin time test remained above the target range in one patient, but below the range in the second before the detection of deep vein thrombosis.

In the adjusted group, 62 per cent of activated partial thromboplastin time result were greater than the target value. This compared with 42 per cent in the fixed dose group ($P<0{\cdot}001$, χ^2 test). The distribution of the mean result for the fixed and adjusted dose patients is given in *Figure 1*. The mean heparin dose for the adjusted patients was greater (94·5 units/kg three times a day), than in the fixed dose group (77·1 units/kg three times a day; $P<0{\cdot}001$; see *Figure 2*).

Postoperative bleeding was assessed by measuring postoperative drainage, the number of units of blood transfused, the change in haemoglobin and the incidence of wound haematoma. Analysis was only possible with the hip replacement groups. None of the above indicators of bleeding showed any significant difference between the fixed and adjusted dose groups.

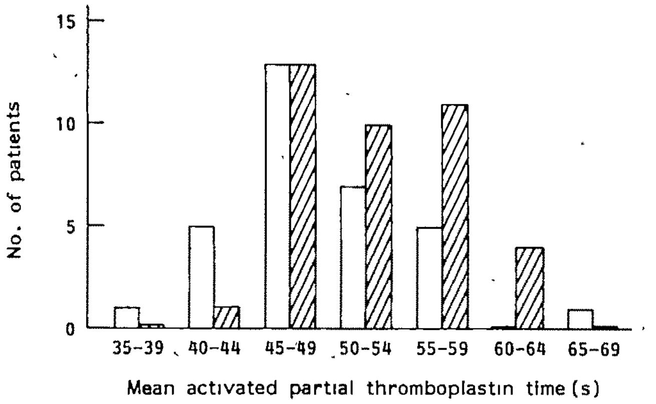

Figure 1 *Distribution of mean activated partial thromboplastin time results.* □, *fixed dose,* ■, *adjusted dose*

Discussion

The administration of fixed low dose subcutaneous heparin has been shown to be effective in the prevention of deep vein thrombosis and pulmonary embolism following major general surgery[5]. However, in certain high risk patients, such as those undergoing hip surgery, the incidence of postoperative venous thrombosis is still unacceptably high[1]. This has led to the consideration of alternative forms of prophylaxis. Alternatives, including the use of low molecular weight heparins[6] and combining low dose heparin with dihydroergotamine, have been recommended.

In a previous study, we provided preliminary data favouring an adjusted rather than fixed low dose regimen with subcutaneous heparin in hip surgery. Maintenance of a minimal prolongation of the activated partial thromboplastin time test was associated with protection from postoperative venous thrombosis without undue haemorrhage[3]. A clinical trial achieving significant benefit with an adjusted dose heparin regimen in hip surgery was subsequently published[4]. However, the mean adjusted dose of 5000 units 8-hourly was compared with a conservative fixed dose of 3500 units 8-hourly. The relative merits of the adjusted dose regimen compared with the conventional fixed dosage regimen of 5000 units 8-hourly therefore required evaluation. Our present study shows that, in hip replacement, adjusted dose subcutaneous heparin significantly improves prophylaxis compared with the fixed dose (5000 units 8-hourly) regimen. The mean heparin dose was considerably increased in the adjusted group. Excessive bleeding might therefore have been expected. The postoperative change in haemoglobin was not significantly different from the fixed dosage regimen. The measured blood loss, the volume of blood transfused and the incidence of wound haematoma were similar in both treatment groups. This indicates that adjustment, although involving a larger dose of heparin, does not increase the risk of excessive bleeding. A safety factor may have been that all patients received the same heparin dose for the first 24 h. In the hip replacement patients dose increments, where necessary, were only made after operation.

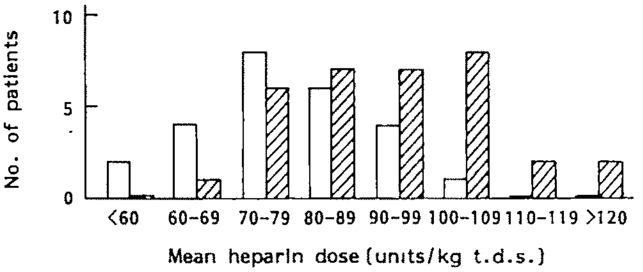

Figure 2 *Distribution of mean heparin dose·* □, *fixed dose,* ■, *adjusted dose*

Alternative techniques may be used to measure blood heparin levels but the activated partial thromboplastin time is the most widely used test for heparin control. We have shown previously that the Manchester activated partial thromboplastin time technique is suitable for monitoring the concentrations of heparin which result from low dose subcutaneous prophylaxis. It does not necessarily follow that equal success in prophylaxis of deep vein thrombosis and prevention of haemorrhage will result from heparin dose adjustment with activated partial thromboplastin time methods less responsive to the heparin effect.

Limitations in the adjusted dose approach are the demands on laboratory and clinical staff. Laboratory control involves precision in the timing and collection of blood samples and dose adjustment to keep the activated partial thromboplastin time test in the required range. Nevertheless, the regimen appears highly rewarding in preventing postoperative deep vein thrombosis during hip replacement.

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Role for prazosin in reducing the development of rabbit intimal hyperplasia after endothelial denudation

Intimal hyperplasia is the universal response to endothelial denudation and occurs after a variety of vascular procedures. In a proportion of cases the smooth muscle cell proliferation may lead to stenosis of the blood vessels. These vessels exhibit increased sensitivity to noradrenaline that can be reduced by the α_1-adrenergic antagonist prazosin. Because the α_1-adrenergic receptor and platelet-derived growth factor (which promotes vascular smooth muscle cell proliferation) act through the same metabolic pathway, it was postulated that α_1-adrenergic blockade might reduce the development of intimal hyperplasia. Twenty-eight New Zealand White rabbits underwent endothelial denudation of the aorta using a Fogarty balloon catheter. Test rabbits were treated with prazosin from the day of operation until they were killed. All rabbits were killed either 1 or 4 weeks after endothelial denudation. Intimal hyperplasia in cross-sections of the aorta was measured using an X–Y digitizer and was standardized in terms of percentage luminal reduction. Prazosin-treated rabbits had significantly less luminal reduction at 1 week (0·75(1·8) versus *9·7(3·1) per cent, mean (s.d.),* P < *0·001) and at 4 weeks (14·7(4·4)* versus *25·3(12·8) per cent,* P < *0·05) than control rabbits. It is concluded that prazosin caused a major reduction in the development of intimal hyperplasia.*

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Following vascular endothelial denudation smooth muscle cells migrate from the media across the internal elastic lamina and then proliferate to form the neointima. This sequence of events, known as intimal hyperplasia, occurs in many clinical conditions. All vein bypass grafts, whether in the aortocoronary position or more peripherally in the arterial circulation, show histological evidence of intimal hyperplasia within 12 months of surgery and as many as 25 per cent of late failures in peripheral vein grafts are a result of this thickening[1]. Following coronary angioplasty the reported incidence of restenosis is 30 per cent at 6 months[2] and after carotid endarterectomy restenosis occurs in 16 per cent at long-term follow-up[3]. Intimal hyperplasia also occurs following embolectomy procedures[4,5], renal transplantation[6] and cardiac transplantation[7].

Recent experimental studies have demonstrated that endothelial denudation and the subsequent development of intimal hyperplasia is accompanied by a selective increase in sensitivity to noradrenaline[8–11]. Increased sensitivity to noradrenaline is associated with an increased affinity in the α_1-adrenergic receptor of vascular smooth muscle cells and an associated increase in turnover in the intracellular phosphatidylinositol cycle[12].

The aetiology of intimal hyperplasia (and its role in the development of atherosclerosis) has recently been reviewed by Ross[13] and the evidence suggests a leading role for platelet-derived growth factor in stimulating vascular smooth muscle cell proliferation. Platelet-derived growth factor is thought to act by increasing turnover in the phosphatidylinositol cycle. By-products of this cycle lead to an increase in intracellular calcium which stimulates protein kinase c to promote a series of phosphorylating reactions leading to cell mitosis[14]. Thus the development of intimal hyperplasia and the associated supersensitivity to noradrenaline are connected through a common pathway: the phosphatidylinositol cycle.

This study was designed to test the hypothesis that selective blockage of the α_1-adrenergic receptors might lead to a reduction in vascular smooth muscle cell mitosis and intimal hyperplasia.

Materials and methods

Twenty-eight male New Zealand White rabbits (3–5 kg) were used. Each rabbit underwent endothelial denudation of the abdominal aorta using a Fogarty balloon embolectomy catheter Fourteen rabbits were treated with prazosin (a specific α_1 antagonist) and the degree of intimal hyperplasia was compared at 1 week and 4 weeks after endothelial denudation with a control group.

Endothelial denudation

The technique used for endothelial denudation has been described previously[9] Anaesthesia was induced using thiopentone (50–100 mg) and maintained with nitrous oxide (2 l/min) and oxygen (2 l/min) The femoral artery was identified through a groin incision and a transverse arteriotomy made. A 4Fr Fogarty catheter (Edwards Laboratories Incorporated, Santa Ana, California, USA) was introduced and advanced proximal to the level of the renal arteries (approximately 16 cm from the groin). The balloon was then inflated and withdrawn to the aortic bifurcation. This was repeated three times and then the femoral artery was ligated and the skin sutured. This procedure resulted in consistently reproducible endothelial denudation of the infrarenal abdominal aorta.

Protocol

All rabbits were caged individually, given water *ad libitum* and fed the normal rabbit chow (Purina, ICN Biochemicals, Cleveland, Ohio, USA) Test rabbits were given a single daily dose of prazosin (Pfizer Ltd , Sandwich, Kent), 4 mg per os, commencing on the morning of the balloon catheter procedure and continuing until the day the animals were killed. The rabbits were killed at either 1 or 4 weeks after endothelial denudation Thus, four groups were available for study

Tissue harvesting

The rabbits were anaesthetized after which the internal jugular vein was cannulated A 4 per cent glutaraldehyde solution was infused at arterial pressure to fix the vasculature *in situ*. A total of 200 ml was infused over a period of 20 min and the aorta was then exposed and clamped at the level of the renal arteries and at the aortic bifurcation This segment of the abdominal aorta was excised and immediately fixed in 3·7 per cent formaldehyde. This technique is a modification of that previously described by Clowes *et al*[15].

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Table 1 *Percentage luminal reduction in rabbit aorta due to intimal hyperplasia*

	Luminal reduction	
	1 Week	4 Weeks
Control rabbits	9·7(3·1)* ($n=6$)	25·3(12·8)† ($n=6$)
Prazosin-treated rabbits	0·75(1·8)* ($n=7$)	14·7(4·4)† ($n=6$)

The results are expressed as mean (s.d.) percentage luminal reduction. *$P<0{\cdot}001$, †$P<0{\cdot}05$ (Mann–Whitney U test)

Histological and morphometrical methods

Tissue blocks of cross-sections of the aorta were cut at a fixed point 2 cm distal to the renal vessels. The tissue blocks were dehydrated and embedded in paraffin. Sections 6 μm thick were cut and mounted on glass slides and were stained with haematoxylin and eosin. A total of six sections were cut from each aorta. The doughnut sections were projected at a standard magnification and the outline of the layers of the vessel wall were then traced on to paper sheets. The luminal surface, internal elastic lamina and the external elastic lamina were used to outline the intima and media. Planimetry of the vessel wall layers measured the surface area of the neointima using an Apple tablet interacting with an IBM personal computer. The mean area of intimal hyperplasia for each of the animals was calculated and the mean area of intimal hyperplasia for each group was then calculated. All area measurements were performed by two observers and the interobserver standard error for individual sections was 5 per cent.

In normal vessels the intima is one cell thick and does not have any significant area and so the luminal cross-sectional area in a normal vessel is that area within the internal elastic lamina. In vessels with intimal hyperplasia the cross-sectional area is reduced in direct proportion to the degree of hyperplasia. The results are, therefore, expressed as the percentage reduction in luminal cross-sectional area due to the intimal hyperplasia.

The Mann–Whitney U test was used for statistical evaluation of the differences in intimal hyperplasia between the control and prazosin-treated groups. Results were considered significant at the $P<0{\cdot}05$ level. Variance was expressed as the standard deviation (s.d.).

Results

At the completion of the study period the mean weight gain for the four groups was similar. One prazosin-treated rabbit and two control rabbits died shortly after the balloon procedure but otherwise the balloon procedure and the prazosin were well tolerated. Thus a total of 25 rabbits were available for study.

As in previous studies using this model, intimal hyperplasia developed throughout the length of the denuded abdominal aorta. However, the intimal hyperplasia was often asymmetrical and, hence, multiple sections from each rabbit were examined.

Rabbits killed at 1 week already showed the early development of intimal hyperplasia with smooth muscle cell proliferation in the neointima. At 4 weeks, however, the degree of hyperplasia had advanced significantly with an approximate tenfold increase in intimal thickness in control rabbits (*Figure 1*). At this stage the neointima was lined by typical endothelial cells.

The prazosin-treated rabbits, both at 1 week and 4 weeks after endothelial denudation, had significantly less intimal hyperplasia than the control rabbits (*Table 1*). At 1 week the cross-sectional area in control rabbit aortas has been reduced by almost 10 per cent but in prazosin-treated rabbits it was reduced by less than 1 per cent. The difference at 4 weeks was also significant with a 25 per cent reduction in control rabbits compared with 15 per cent in prazosin-treated rabbits. Apart from the reduction in intimal thickness in prazosin-treated rabbits there was no difference detectable in the morphological appearances of the intima in treated and control rabbits.

Discussion

Occlusion of vessels following vascular procedures may be due to several factors. After procedures such as vein bypass grafting, embolectomy, angioplasty and endarterectomy early occlusion is related to platelet aggregation and/or technical errors. Later occlusion is related to the smooth muscle cell proliferation of intimal hyperplasia in a significant number of cases[1–3]. Intimal hyperplasia also predisposes to the early reapperance of atherosclerosis which is often of a particularly aggressive nature[1,7,16,17]. Thus, the unfortunate irony that our currently available techniques for managing atherosclerotic disease may themselves predispose to recurrence of the same disease process.

The rabbit is a suitable model to investigate intimal hyperplasia as endothelial denudation results in predictable smooth muscle cell proliferation[4,5,9]. A recent report has convincingly demonstrated that a similar response occurs in humans after the passage of an embolectomy balloon catheter[18]. It is well recognized that intimal hyperplasia is prevalent at anastomotic sites (in particular at the distal anastomosis of bypass grafts) and this is responsible for the continuing attention to improved surgical technique[19–21]. However, endothelial denudation is inevitable with currently available techniques and so attention has been directed at possible pharmacological intervention in the prevention of intimal hyperplasia.

While the antiplatelet agents, aspirin and dipyridamole, have been extensively investigated, the results have been equivocal and also appear to be dependent on the species studied. Hagen

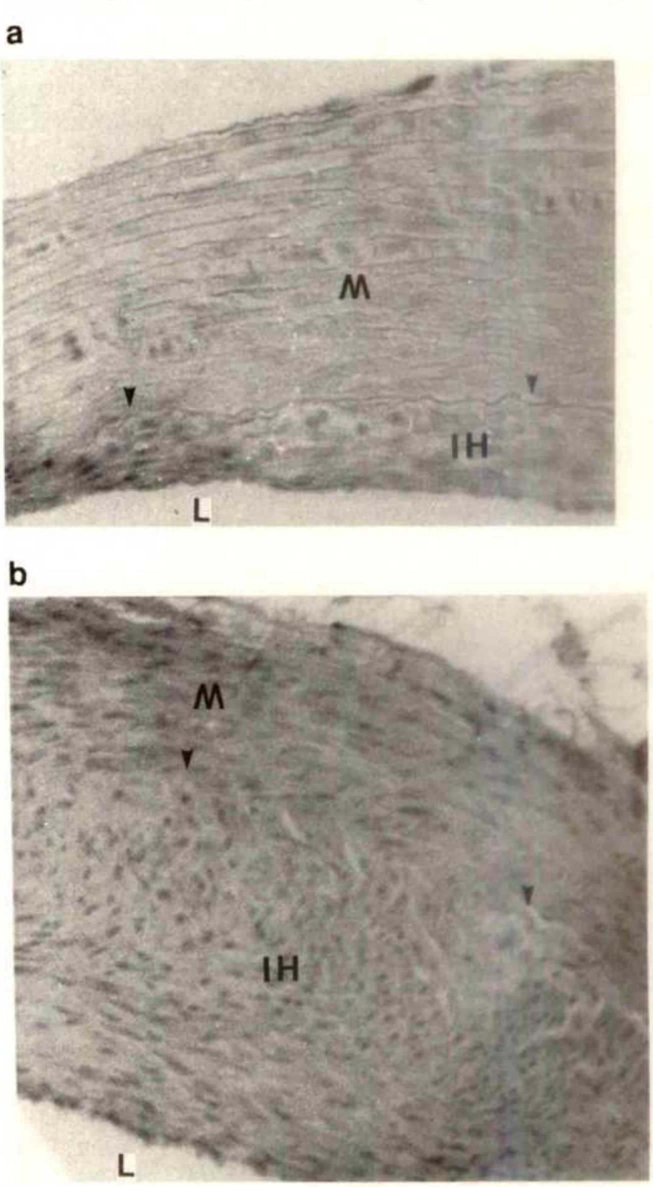

Figure 1 *Photomicrographs of* **a** *prazosin-treated and* **b** *control rabbit aorta 4 weeks after endothelial denudation. The prazosin-treated rabbit shows less intimal hyperplasia than the control rabbit. M, media; IH, intimal hyperplasia; L, lumen; the arrows demonstrate the internal elastic lamina. (Haematoxylin and eosin, ×40)*

et al.[22] and McCann *et al.*[23] have shown a reduction in intimal hyperplasia in primates with synthetic and autogenous vein grafts. Metke *et al.*[24] have also shown a reduction in intimal hyperplasia is canine coronary bypass vein grafts using aspirin and dipyridamole. However, Radic *et al.*[25] showed no benefit from antiplatelet therapy in rabbit aorta subjected to endothelial denudation while Murday *et al.* reported an increase in intimal hyperplasia in rabbit vein grafts[26]. Finally, while Chesebro *et al.* have demonstrated increased patency of coronary artery vein bypass grafts in human[27], other studies have shown no benefit from antiplatelet treatment[28,29]. These confusing and contradictory results are related to many factors such as the dosage of aspirin, the introduction of treatment before or after surgery and platelet function and response to aspirin in different species. For these reasons we chose not to compare prazosin with antiplatelet therapy in reducing rabbit intimal hyperplasia.

The results of this study suggest that prazosin reduces the development of intimal hyperplasia both at an early and late stage. It is known from previous studies[9] that following endothelial denudation the rabbit develops maximal smooth muscle cell proliferation within 4 weeks. Further reduction in cross-sectional area after this time is likely to be due to lipid incorporation and the development of atherosclerotic plaques. We now have evidence to suggest that prazosin will also reduce the development of this process[30].

Extensive experimental and some clinical evidence now exists to show that both atherosclerosis[31–34] and intimal hyperplasia[8–12] alter arterial function by increasing contractility in response to such naturally occurring agonists as histamine, serotonin and noradrenaline. In particular, rabbit aorta with intimal hyperplasia is supersensitive to noradrenaline and this is counteracted by the administration of prazosin[9]. Thus, if prazosin proves to be effective in reducing intimal hyperplasia in clinical studies, it may be preferred as a prophylactic agent because it would also reduce the increased sensitivity of these vessels to noradrenaline. Furthermore, it is a drug which already has an accepted place in clinical practice in the treatment of hypertension. However, the role of prazosin in preventing intimal hyperplasia in coronary artery bypass grafts is open to question as the coronary arteries have a mixed α- and β-adrenergic receptor population whereas the peripheral arterial circulation has a relatively pure α_1-adrenergic receptor population.

The usual caveats regarding the relevance of animal studies in the clinical sphere apply to the proposed use of prazosin in reducing intimal hyperplasia. However, we feel that this now deserves investigation and plan to proceed with clinical studies.

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Platelet aggregability after endoscopic intravariceal injection of 5 per cent ethanolamine oleate into oesophageal varices

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Platelet aggregability and the coagulative and fibrinolytic systems were examined in 45 patients who underwent endoscopic injection sclerotherapy for oesophageal varices. Five per cent ethanolamine oleate, the sclerosant used, was injected into the oesophageal varices. There were significant increases in the concentrations of fibrinopeptide A, fibrinopeptide B-β-15–42 and fibrin degradation products-E after the sclerotherapy. At 1 h after the sclerotherapy the mean(s.e.m.) platelet aggregation was significantly suppressed to 71·9(4·2) per cent of that before the treatment ($P<0.01$)*. There was a gradual recovery within 1 week to the same level seen before the sclerotherapy. Thomboxane* B_2 *and 6-keto-prostaglandin* $F_{1\alpha}$*, both stable products of thromboxane* A_2 *and prostacyclin respectively, showed significant temporary increases after the sclerotherapy* ($P<0.01$)*. The peak increase in the level of thromboxane* B_2 *was noted within 1 h after the sclerotherapy and earlier than that for 6-keto-prostaglandin* $F_{1\alpha}$*. This increased ratio of prostacyclin and thromboxane* A_2 *may be related to the marked limitation in platelet aggregation.*

Keywords: Endoscopic injection sclerotherapy, 5 per cent ethanolamine oleate, platelet aggregability, prostacyclin, thromboxane A_2

Since Crafoord and Frenckner[1] first reported endoscopic injection sclerotherapy for oesophageal varices in 1939, this technique has been used with excellent results[2]. The injection of sclerosants into varices leads to a thrombogenesis[3], through chemical damage to the vessel wall. Nevertheless, the precise mechanism of the haemostatic effect of sclerotherapy has not been elucidated. There are a few reports on the coagulative and fibrinolytic systems after sclerotherapy[4–6] but platelet aggregability, *per se*, has not been fully investigated, despite it being the first step in coagulation[7]. We examined platelet aggregability in relation to prostaglandin activity after the intravariceal injection of 5 per cent ethanolamine oleate for oesophageal varices in patients with cirrhosis.

Patients and methods

Patients

This study was performed on 45 Japanese patients with oesophageal varices caused by cirrhosis All were admitted to the Second Department of Surgery, Kyushu University Hospital from June to December 1987 Thirteen patients were cases of alcoholic cirrhosis and 32 were non-alcoholic related cases (primary biliary cirrhosis in one and the others had posthepatitic cirrhosis) There were 31 men and 14 women in the series, 28 were elective and 17 were prophylactic. The mean(s d) age was 55·5(9·8) years (range 33–77 years). According to the modified Child's classification[8], 13 were Child's grade A, 15 were grade B and 17 were grade C Mean(s.e.m.) retention rate of indocyanine green at 15 min was 37 4(13 4) per cent in all patients.

Methods

Procedure of endoscopic injection sclerotherapy

Endoscopic injection sclerotherapy was performed using a transparent over-tube (K-S tube, Olympus Optical Company, Tokyo, Japan)[9] for a rapid, safer injection in the initial session and the free-hand technique was used in the following sessions The instrument used was the GIF-Q series (Olympus Optical Company). The sclerosant, 5 per cent ethanolamine oleate, was injected directly into the oesophageal varices through a 21G needle at the initial and second sessions of endoscopic injection sclerotherapy At 1-week intervals sclerotherapy was repeated until all the varices were eradicated. In all sessions of endoscopic injection sclerotherapy, the patients were given diazepam (5 mg) and pentazocine (30 mg) intravenously.

Blood samples

Blood samples were collected from the peripheral veins into plastic syringes, with the patients in a resting state. The samples were separated immediately and handled as described later The samples were collected in the early morning soon after sclerotherapy and 30 min, 1 h and 1, 2 and 6 days later.

Platelet aggregation

Platelet aggregation was examined using the Born–O'Brien method[10,11] and an aggregometer (NKK-Hematracer, Model PAT-4M, SSR Company Ltd , Tokyo, Japan). A 13 5-ml sample of blood was added to a silicon coated tube containing 1·5 ml of 3 8 per cent sodium citrate. Platelet-rich plasma was obtained by immediate centrifugation of the citrated blood at 850 r.p.m. for 7 min at 20°C. Platelet-poor plasma was prepared by centrifuging the residual plasma at 1850 r p m for 5 min at 20°C. The aggregating agent was adenosine diphosphate with a final concentration of 8 μmol The aggregation was measured for the maximum change in light transmission divided by the span of the original upper and lower limits set with platelet-poor plasma and platelet-rich plasma. All samples were tested twice within 2 h of collection.

Fibrin degradation products-E

Fibrin degradation products-E was measured by latex photometric immunoassay (LPIA)[12] using kits of LPIA-1 (Mitsubishi Chemical Industries Ltd , Tokyo, Japan). The serum was obtained from blood drawn into a Trasylol (Bayer UK Ltd., Newbury, UK) solution with a final concentration of 500 units/ml by centrifuging at 3000 r p.m. for 10 min, at room temperature

Radioimmunoassay

Plasma levels of 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2, stable catabolites of prostacyclin and thromboxane A_2 respectively, were determined by radioimmunoassay[13], as were fibrinopeptide A and fibrinopeptide B-β-15–42[14].

Other laboratory tests

Other laboratory tests, including prothrombin time, fibrinogen and

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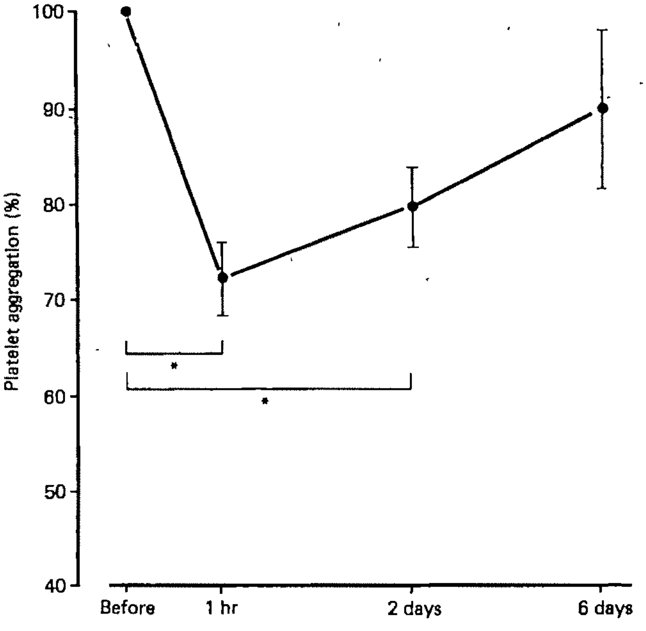

Figure 1 *Platelet aggregability was significantly suppressed at 1 h and 2 days after endoscopic injection sclerotherapy in 24 patients. Return to the preinjection level occurred on the sixth day. The vertical bars represent mean(s.e.m.).* *$P<0·01$ *(Student's* t *test)*

antithrombin III concentrations, partial thromboplastin time and platelet count, were performed in the Central Laboratory of the Kyushu University Hospital.

Statistical method

Results are expressed as mean(s.e.m.). All statistical comparisons for significance were carried out using Student's t test and a P value $<0·05$ was considered significant.

Results

Oesophageal varices were successfully eradicated in all 45 patients. The average dose of ethanolamine oleate injected into varices at the initial session was 21·7(4·6) ml. No major complications occurred. Minor temporary side-effects were retrosternal pain and low grade fever.

Platelet aggregation

One hour after endoscopic injection sclerotherapy the values of platelet aggregation significantly decreased to 71·9(4·2) per cent of that before treatment ($P<0·01$; *Figure 1*). The decrease was 79·6(4·2) per cent on the second day after injection and by the sixth day the value was close to the level seen before sclerotherapy. There was no significant difference between the degree of decrease of platelet aggregation and modified Child's classification.

Fibrinopeptide A and fibrinopeptide B-β-15–42

The concentration of fibrinopeptide A increased from the pretreatment value of 2·9(0·5) ng/ml to 7·6(1·5) ng/ml, 1 h after endoscopic injection sclerotherapy ($P<0·01$), and returned to the pretreatment level within 2 days (*Figure 2*). One hour after endoscopic injection sclerotherapy, fibrinopeptide B-β-15–42 level also showed a significant temporary elevation.

Thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$

Thromboxane B_2 significantly increased soon after endoscopic injection sclerotherapy, compared with the concentration before injection ($P<0·01$; *Figure 3*). The peak thromboxane B_2 level occurred soon after injection and returned to the preinjection level on the second day. The concentration of 6-keto-prostaglandin $F_{1\alpha}$ also increased after endoscopic injection sclerotherapy, however, the peak occurred 1 h later and by 2 days the level had almost returned to that recorded before injection.

Other laboratory data

The concentration of fibrin degradation products-E significantly increased to 191·9(33·3) ng/dl 1 h after endoscopic injection sclerotherapy (*Figure 4*). No significant change was observed in the values of antithrombin III, partial thromboplastin time and prothrombin time. Platelet count and fibrinogen values gradually increased after sclerotherapy; the platelet count was significantly increased on the sixth day ($P<0·01$). Fibrinogen levels significantly increased 1 h after endoscopic injection sclerotherapy ($P<0·01$).

Discussion

Disseminated intravascular coagulation is one possible complication of sclerosing oesophageal varices, particularly when intravariceal injections are given to cirrhotic patients with abnormal coagulative and fibrinolytic functions. Bernardi *et al.*[15] reported that endoscopic injection sclerotherapy did not lead to disseminated intravascular coagulation although transient activation of coagulative and fibrinolytic systems did occur. With a significant decrease in platelet count, an almost complete reversion was noted 18 h after endoscopic injection sclerotherapy. Our findings of increased levels of fibrinopeptide A and fibrinopeptide B-β-15–42 within 1 h after treatment also suggest activation of coagulative and fibrinolytic systems[14,16]. Platelet counts showed no significant change 1 day after endoscopic injection sclerotherapy and disseminated intravascular coagulation did not occur. However, platelet

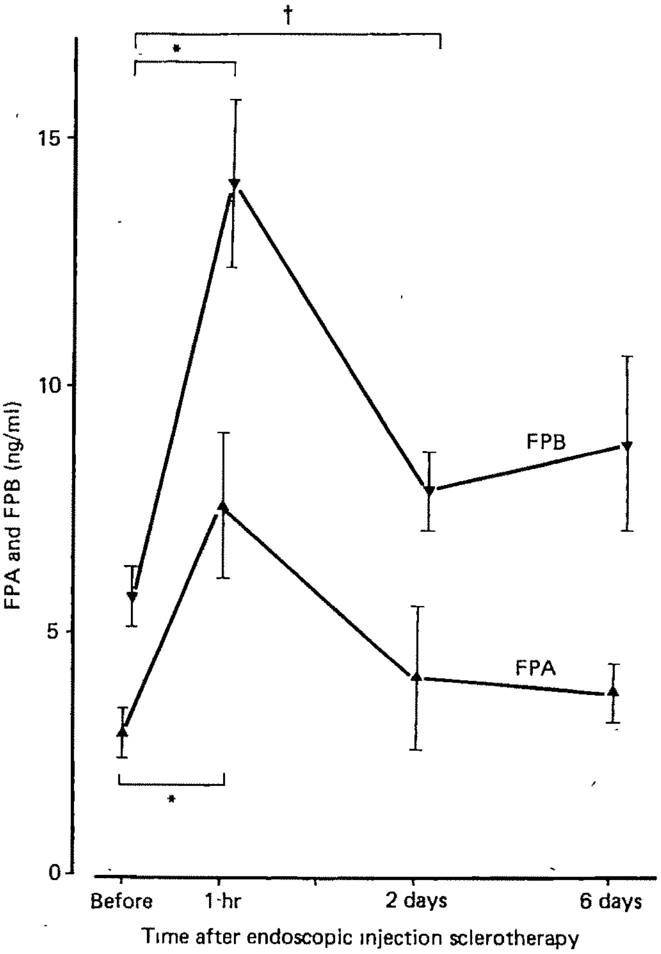

Figure 2 *Levels of fibrinopeptide A (FPA) and fibrinopeptide B-β-15–42 (FPB) were both significantly increased 1 h after endoscopic injection sclerotherapy, and fibrinopeptide B-β-15–42 was significantly increased even 2 days later, in 23 patients. The vertical bars represent mean(s.e.m.).* *$P<0·01$, †$P<0·05$ *(Student's* t *test)*

aggregability was significantly suppressed 1 h after injection. This suppression seems to have an important function in coagulative and fibrinolytic systems as platelet aggregation is the first step in these events. This suppression presumably inhibits deterioration of coagulative and fibrinolytic systems leading to disseminated intravascular coagulation.

In considering why platelet aggregation is significantly suppressed 1 h and even 2 days after endoscopic injection sclerotherapy, at least three factors have to be considered: (1) that coagulative factors such as factor XII[17] may be exhausted by activation of the coagulative and fibrinolytic systems; (2) that suppressive substances such as prostacyclin and fibrin degradation products are produced to protect against thrombus formation; and (3) that oleic acid, present in ethanolamine oleate, may directly suppress platelet aggregation18.

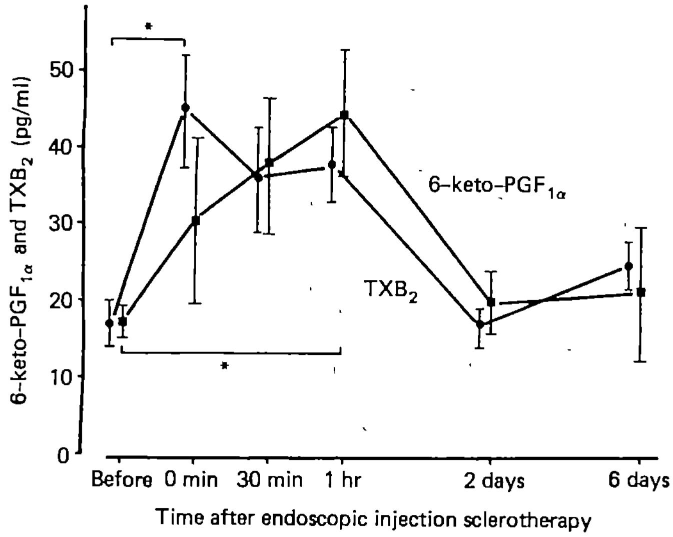

Figure 3 *The level of 6-keto-prostaglandin* $F_{1\alpha}$ *(6-keto-PGF*$_{1\alpha}$*) was significantly increased after 1 h after endoscopic injection sclerotherapy and that of thromboxane* B_2 *(TXB*$_2$*) was significantly increased soon after 1 h in 13 patients. The vertical bars represent mean(s.e.m.),* *$P<0{\cdot}01$ *(Student's* t *test)*

If coagulative factors had been exhausted then decreases in these factors would lead to a prolongation of partial thromboplastin time[19]. However, no significant prolongation occurred after endoscopic injection sclerotherapy, as was noted in other studies[5,6,15]. Fibrin degradation products and oleic acid also protect against platelet aggregation[18,20]. However, both require far higher concentrations to inhibit aggregation than were present in our study[18,20].

On the other hand, the concentration of 6-keto-prostaglandin $F_{1\alpha}$, a metabolite of prostacyclin, significantly increased after endoscopic injection sclerotherapy. This metabolite is most effective in suppressing platelet aggregation[21] as it elevates cyclic-adenosine monophosphate levels in the platelets and inhibits the release of platelet granules. Thromboxane B_2, a potent substance which induces aggregation[22], also increased in concentration after endoscopic injection sclerotherapy. The ratio of prostacyclin to thromboxane A_2 is presumably important in the suppression of platelet aggregation Thromboxane A_2 is released concomitantly with platelet aggregation after treatment, while prostacyclin is produced secondary to the release of thromboxane A_2 and stimulation of the vascular endothelium[23]. Some of the ethanolamine oleate injected enters the systemic circulation[24] and may stimulate the peripheral vascular endothelium; it does, however, injure the vascular endothelium at the site of injection[3]. The stimulation by ethanolamine oleate

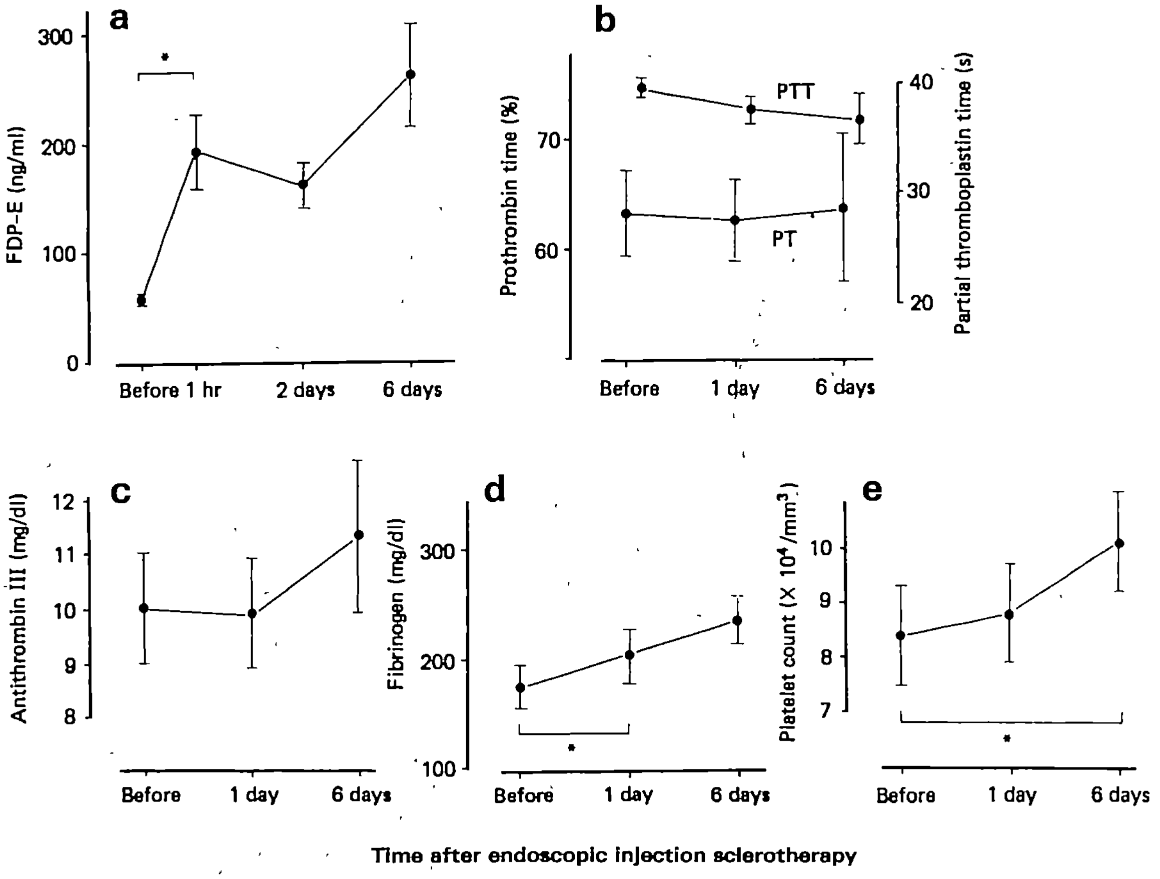

Figure 4 **a** *Fibrinogen degradation products-E (FDP-E) level,* **b** *prothrombin time (PT) and partial thromboplastin time (PTT),* **c** *antithrombin III level,* **d** *fibrinogen level and* **e** *platelet count before and after endoscopic injection sclerotherapy. Fibrin degradation products-E, fibrinogen and platelet count significantly increased in 29 patients. The vertical bars represent mean (s.e.m.);* * $P<0{\cdot}01$ *(Student's* t *test)*

presumably results in a rapid increase in production of prostacyclin in the peripheral circulation. The peak increase in concentration of thromboxane A_2 appears within 1 h, while prostacyclin increases 1 h after endoscopic injection sclerotherapy. The ratio of prostacyclin to thromboxane A_2 increases after the peak of thromboxane A_2 and is greater than that seen before endoscopic injection sclerotherapy. As these changes in prostacyclin and thromboxane A_2 are consistent with changes in platelet aggregation after endoscopic injection sclerotherapy, the production of prostaglandins may explain why platelet aggregation is greatly suppressed after injection.

In conclusion, our study suggests that platelet aggregation after intravariceal injection of 5 per cent ethanolamine oleate was significantly suppressed by a humoral response. Increase in the ratio of prostacyclin to thromboxane A_2 might prevent or at least inhibit the deterioration of the coagulative and fibrinolytic systems after endoscopic injection sclerotherapy.

Acknowledgements

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Transabdominal gastro-oesophageal devascularization and oesophageal transection for bleeding oesophageal varices

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Fifty consecutive unselected patients presenting with acute haematemesis and melaena from endoscopically confirmed bleeding oesophageal varices were treated by one-stage transabdominal oesophageal transection with gastro-oesophageal devascularization and splenectomy. According to Child's classification, 15 were Grade A, 29 Grade B and six Grade C. The mortality rate was 10 per cent. Postoperative complications included gastric fundal leak (4 per cent), pleural effusion (4 per cent), subphrenic abscess (2 per cent), atelectasis (2 per cent) and pneumothorax (2 per cent). Although five patients (10 per cent) complained of transient dysphagia during follow-up, only one (2 per cent) presented evidence of stricture at the site of oesophageal transection. Clinical encephalopathy was not present in the surviving patients in the postoperative period. No recurrence of bleeding has been recorded in the surviving patients over a follow-up period of 2–3 years.

Keywords: Oesophageal transection, gastro-oesophageal devascularization, bleeding oesophageal varices

Portal hypertension with oesophageal varices is the commonest cause of acute gastrointestinal bleeding in Saudi Arabia and reflects the high incidence of schistosomiasis and hepatitis B infection in our patient population. The objective of treatment is to arrest the immediate haemorrhage, and ideally the method employed should have a minimal initial risk of morbidity and mortality and should avoid the long-term problem of rebleeding. Over the last three decades many methods have been advocated including porta azygos disconnection[1], oesophageal sclerotherapy[2], oesophageal transection[3,4], and porta caval decompression by shunt procedures[5], but the search for the ideal treatment continues. This report concerns the use of combining oesophagogastric devascularization with oesophageal transection performed transabdominally as a one-stage procedure.

Patients and methods

At the Riyadh Central Hospital all patients with acute gastrointestinal tract bleeding are admitted to the Haematemesis/Melaena Unit After appropriate resuscitative measures urgent gastrointestinal endoscopy is performed for diagnostic purposes Resuscitative measures include administration of fresh blood, fresh frozen plasma and cold gastric lavage. In patients who continue to bleed vasopressin therapy or tamponade using a Sengstaken–Blakemore tube are employed Between April 1985 and May 1986, 352 patients were admitted to the Unit and of these 116 (33 per cent) were diagnosed as bleeding from oesophageal varices Definitive treatment was undertaken by the one of the three surgical units on duty at the time of the patient's admission. Of these 116 patients, 58 were admitted under the care of the authors of this report Eight patients whose bleeding ceased during the early management refused further treatment and left the hospital against medical advice They were subsequently lost to follow-up leaving 50 patients who were treated surgically These 50 patients form the basis of this report, and all underwent transabdominal gastro-oesophageal devascularization and oesophageal transection

The age range of the patients was 21–75 years and only one patient was female Twenty-eight patients presented with haematemesis, 18 with both haematemesis and melaena and four patients with melaena alone In 34 patients with severe continuing haemorrhage, the surgical procedure was performed on the day of admission on an emergency basis. In the remaining 16 patients initial stabilization was satisfactory with arrest of haemorrhage and the operation was undertaken on the next elective operating schedule Eleven patients had a history of previous bleeding that had been treated elsewhere Five of these had undergone a Hassab devascularization procedure, another five had multiple sessions of sclerotherapy and one patient had a Warren distal splenorenal shunt.

Table 1 shows the grouping of the 50 patients according to Child's classification. *Table 2* shows the endoscopic grading of the oesophageal varices assessed by a subjective grading from I to IV corresponding to the method described by Paquet[6]. Eleven (22 per cent) patients had a positive surface antigen test for hepatitis B infection Histological examination of the operative liver biopsies showed schistosomiasis in 28 cases, posthepatitic changes in nine cases, a combination of schistosomiasis with posthepatitic changes in 12 cases and alcoholic cirrhosis in one case (*Table 3*) The diagnosis of cirrhosis was made when fibrosis was associated with structurally abnormal parenchymal nodules, and was classified as micronodular or macronodular depending on whether the nodules were less or more than 3 mm in diameter Cirrhosis was considered posthepatitic when specific features including ground glass cells and positive viral antigen were present, and alcoholic when fatty change and Mallory bodies were seen.

Diagnosis of schistosomiasis

The diagnosis of schistosomiasis was based on the following:

1 Observation of the parasite, ova or the black pigmentation in the portal spaces or in the Kupffer cells
2. The presence of typical fibrosis including wire, irregular thin-walled vascular spaces with or without evidence of schistosomiasis in other tissues, e.g. oesophageal tissue
3 The presence of granulomatous changes associated with parts of the eggs.

When schistosomiasis was associated with cirrhosis regenerative changes and architectural distortion were noted in all cases. In about 50 per cent of cases the parasite or the ova were seen while in the other cases only indirect evidence of schistosomiasis was found

Operative procedure

All patients were operated on by the same surgical team The amount of intraoperative blood transfusion and the time taken for the operative procedure were recorded Laparotomy was carried out through a bilateral subcostal incision extending to the anterior axillary line on the left side Gastric devascularization and splenectomy was performed as in the Hassab procedure. This involves both curvatures of the stomach preserving only the right gastric and right gastroepiploic vessels Oesophageal devascularization was performed up to the diaphragmatic hiatus by ligating all the collateral vessels. From 4 to

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Table 1 *Grouping of patients according to Child's classification*

Child's classification	Number of patients	Hepatitis B antigen positive	Histopathology of liver		
			Schistosomiasis	Micronodular	Alcoholic
A	15	2	7	8	0
B	29	5	19	10	0
C	6	4	2	3	1
Total	50	11	28	21	1

Table 2 *Endoscopic grading of the varices*

Grade	Preoperative	Postoperative
I	0	13
II	4	28
III	15 } 46	4
IV	31	0
Total	50	45

5 cm of thoracic oesophagus was exposed and its feeding vessels were either cauterized or occluded with clips. Both vagi were divided. Through a small anterior gastrotomy a disposable curved EEA® stapler (US Surgical Corporation and Auto Suture UK, Ascot, UK) was introduced into the lower oesophagus. The size ranged from 25 to 31 mm. A purse string suture was tied 1·5–2 cm above the oesophagogastric junction and the instrument then fired to complete the closed transection.

The gastrotomy incision was closed with a TA 55® stapler (US Surgical Corporation and Auto Suture, UK) and the procedure completed with a Heineke–Mikulicz pyloroplasty. The abdomen was drained with two Yeates' drains, one placed in the splenic bed and the other near the pyloroplasty site. On the third postoperative day the patient was given dilute methylene blue to swallow, the appearance of the methylene blue from the drains was indicative of a leak. Gastrografin® swallow (Schering Health Care Ltd., Burgess Hill, UK) studies were done on the fifth postoperative day to demonstrate patency of the oesophageal anastomosis or the presence of any leakage.

Results

Operative difficulties

Intraoperative bleeding (generalized oozing) due to low platelet count, prolonged prothrombin time and the presence of jaundice was overcome by the liberal use of fresh frozen plasma and platelet concentrate during surgery. Considerable oedema of the lower oesophagus was encountered in one patient because of injection sclerotherapy performed at another centre 5 days before admission to our unit. In this patient an EEA size 28 stapler was used to transect the oesophagus, and this was followed by considerable bleeding from the site of transection. Inspection of the transected doughnut showed partial transection of the thickness of the oesophageal wall. This problem was overcome by re-enforcing the anastomotic line with Vicryl® (Ethicon Ltd., Edinburgh, UK) sutures. In another patient there was considerable loss of blood from the left drain despite a normal clotting profile. Re-exploration revealed active bleeding from the splenic bed and this was dealt with accordingly. Symptomatic gallstones were found in one patient and cholecystectomy was added to the procedure. In another patient a hard mass was felt in the gallbladder wall near the fundus. This was thought to be a tumour of the gallbladder. Cholecystectomy with wedge resection of the gallbladder bed was performed. Histopathological examination revealed bilharzial granuloma from the liver infiltrating the gallbladder wall.

Postoperative morbidity

Twenty-one patients (42 per cent) showed pyrexia of no definite pattern during the postoperative period. Ten of these patients had chest infection proved by sputum cultures, two patients had pleural effusion and one patient had a subphrenic collection. The fever in these patients subsided after appropriate treatment. The remaining eight patients were pyrexic for 10–20 days without obvious cause and this subsided spontaneously without treatment.

There was no leakage at the oesophageal transection site in this series. Minor gastric leakage was encountered in two patients. In one patient a leak from the fundus of the stomach was attributed to extensive devascularization and consequent patchy necrosis. This responded well to conservative treatment. In the other patient the gastric leak occurred after draining a subphrenic collection through a posterior approach that had resulted in a left-sided pneumothorax and atelectasis. This patient was also managed conservatively with total parenteral nutrition, and was well at discharge home on the 87th postoperative day.

Mortality

Forty-four patients left the hospital 10–32 days after operation (mean 24 days). One patient left on the 87th postoperative day. The remaining five patients died during the first 2 weeks of the postoperative period, giving a mortality rate of 10 per cent. Four of those who died were patients in Child's Group C. They developed progressive hepatic failure; in one of them death was precipitated by a pulmonary embolism on the fifth postoperative day. The fifth patient (Child's Group B), who had poorly controlled diabetes and underwent emergency surgery, developed acute renal failure, later complicated by progressive hepatic failure, he died on the 10th postoperative day. Postoperative deaths occurred in one of 28 schistosomiasis patients, three of nine hepatitic patients and in one of 12 patients with combined pathology.

Follow-up

The 45 surviving patients who were under regular follow-up for a period of 2–3 years showed no symptoms or signs of hepatic encephalopathy. Six patients complained of dysphagia; only one required repeated dilatation and he remained symptom-free after the fourth dilatation session. The remaining five patients improved gradually without treatment. One patient complained of heartburn, which proved to be due to reflux oesophagitis and which reponded well to treatment with antacids. This particular patient had a very low oesophageal transection at the oesophagogastric junction.

None of the surviving 45 patients has rebled during the follow-up period. All the patients were examined by upper gastrointestinal endoscopy at 4-monthly intervals during the follow-up period. *Table 2* shows the regression in the grading of the varices.

Discussion

Bleeding from oesophageal varices presents a difficult management problem because of recurrent bleeding and its associated high mortality rate. Numerous operative procedures intended to ablate, disconnect or decongest the dilated venous collaterals of the oesophagogastric region have been devised. Sugiura and Futagawa[7] reported their technique of transthoracic oesophageal devascularization, transection and splenectomy in 1973. Later they reported the results of 276 patients dealt with over a period of 10 years[8], 60 of whom underwent the surgery for prophylactic reasons. None of our patients had surgery for prophylactic reasons. Hassab developed his own non-shunt technique and reported 355 cases in 1967[9]; of these, 151 patients were non-bleeders. By 1970 Hassab had undertaken 605 operations and reported the follow-up of 232 patients[10]. Of these, 92 patients had undergone the procedure for prophylactic reasons.

The rebleeding rate during the immediate postoperative or follow-up period is an important evaluation factor. Hassab reported a 2 per cent fatal rebleeding rate in the immediate postoperative period[9]. In a later report[11] the recurrent bleeding rate was 7 per cent and two patients required reoperation. Seven other patients were described as having had minor bleeds during follow-up. Sugiura reported a rebleeding rate of 12 per cent after Hassab's operation and 3 per cent after his own procedure[7], while Gouge and Ranson[11] reported a higher rebleeding rate of 37 per cent after the Sugiura procedure. This can be explained on the basis of the 'intact' posterior wall of the oesophagus which remains after the Sugiura procedure[8,11], while Hassab's operation does not interrupt the submucosal and intermuscular variceal veins[11,12].

Oesophageal transection alone may not prevent recurrent bleeding as ws observed by Spence[13] and Spence and Johnston[14,15]. In their procedure only the left gastric vessels were ligated and Johnston[16] reported a series of 80 patients with a rebleeding rate of 5 per cent. In a more recent series of 100 patients reported in 1985, three patients rebled in the immediate postoperative period and 11 patients rebled during the follow-up period[14]. Cooperman *et al.*[17] encountered no rebleeding in their five patients having oesophageal transection using the EEA stapling gun. In our series of 50 patients there was no rebleeding either during the immediate postoperative period or during the 2–3 years of regular follow-up. Da Silva *et al.*[18] have undertaken a randomized trial of oesophagogastric devascularization, splenorenal shunt and distal splenorenal shunt for patients with bleeding oesophageal varices due to schistosomiasis. However, the type of non-shunt devascularization procedure undertaken by these authors differs from our own in that the oesophagus is not transected; hence, a comparison cannot be drawn between the operative procedures.

In terms of operative results, none of the patients undergoing oesophagogastric devascularization had portosystemic encephalopathy as was the experience of Da Silva *et al.*[18]. However, the rate of rebleeding reported in their series was 13·3 per cent compared with nil in our series. Again we emphasize that because the submucous and intramuscular venous channels are not interrupted by their procedure, a significant rate of rebleeding can be expected. In Da Silva's series all the patients reported had schistosomal pathology[18], while in our series 44 per cent of patients had non-schistosomal pathology.

The operative time required to perform the procedure is of paramount significance in these seriously ill patients. Comparison with shunt surgery cannot be valid and our ablative procedure should be compared only with other ablative procedures. The mean operative time for Hassab's procedure is not reported[9,10], while in the Sugiura procedure the average operation time was reported as 9 h 30 min[11]. Other authorities believe that this extensive procedure is probably unnecessary for some and too dangerous for other patients[19]. The adverse effects of the length of the operative time on survival is significant. Operative procedures exceeding 6 h had a mortality rate of 70 per cent compared with 33 per cent for those taking less than 6 h[20]. In our series the average time required to perform the procedure was 3 h 45 min, with a minimum of 2 h 30 min and a maximum of 4 h 30 min.

The 'in-hospital' stay period in this series was between 10 and 32 days (mean 24 days). Only one patient stayed for 87 days because of a subphrenic collection, leak and chest infection. The average in-hospital stay for the Sugiura procedure is 30 days with a chest complication rate of 20 per cent[11], as opposed to 8 per cent in the present series. Although dysphagia occurred in six patients (12 per cent) only one required dilatation while the remaining five became asymptomatic spontaneously. This compares well with the findings in other series[14,16,21,22]. Leakage from the anastomotic site did not occur in any of our patients and the two gastric leaks detected give an incidence of leakage comparable to that of Johnston[16]. Our mortality rate of 10 per cent compares favourably with rates in other series which range from 14 to 25 per cent[9,11,19]. The five deaths in this series occurred during the postoperative period and were mainly due to liver failure The satisfactory outcome of combined gastric devascularization and oesophageal transection for bleeding oesophageal varices has encouraged us to persist with the method which is worthy of further trial and evaluation

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Sham feeding for testing gastric secretory capacities before and after parietal cell vagotomy

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The usefulness of acid secretory data collected during a modified sham-feeding (MSF) test was examined in 50 patients suffering from duodenal ulcer before and after parietal cell vagotomy. In these patients basal acid output pentagastrin-stimulated acid output and MSF-stimulated acid output were measured. Preoperative MSF-stimulated acid output was found to be correlated with preoperative basal acid output, and postoperative MSF-stimulated acid output was correlated with both preoperative basal acid output and postoperative basal and pentagastrin-stimulated acid outputs. The addition of preoperative MSF-stimulated acid output to preoperative pentagastrin-stimulated acid output did not noticeably increase the close relationship between the latter and postoperative pentagastrin-stimulated acid output. It is concluded that basal and MSF-stimulated secretory rates overlap. Therefore, it is suggested that in both preoperative and postoperative conditions the addition of the sham-feeding test to the more simple basal and pentagastrin-stimulated studies could be discarded.

Keywords: Duodenal ulcer, sham feeding, gastric function tests

The modified sham-feeding (MSF) test was introduced 8 years ago[1–3] as a simple, harmless and efficient vagal test, generally associated with the measurement of acid secretion but also with pepsin output[4] and plasma pancreatic polypeptide concentrations[5–9]. Combining these exocrine and endocrine parameters or not, authors have proposed MSF in an attempt to check the completeness of parietal cell vagotomy[2,10–14] or to assess vagal tone[3,8,15] to predict ulcer recurrence[11,16] or ulcer activity[4]. However, whatever the parameter considered, the usefulness of the MSF test, with respect to any of these objectives, remains debatable. The present study was designed to investigate whether there is any advantage in adding the MSF-stimulated acid secretory data to the classical basal acid output and pentagastrin-stimulated acid output parameters for the appreciation of the secretory pattern in duodenal ulcer patients both before and after parietal cell vagotomy.

Patients and methods

Patients

From March 1982 to August 1986, 50 patients (42 men, eight women) of mean age 39·7 years (range 18–68 years) with well established uncomplicated duodenal ulcers were examined 1 week before and 2 months (mean 64·7 days) after parietal cell vagotomy.

Secretory procedures

The tests were performed after an overnight fast, any anticholinergic or antisecretory medication being withdrawn at least 48 h before the study.

A multiple-lumen nasogastric tube was positioned in the fundus for gastric juice collection. Residual gastric contents were discarded, a 100-ml water recovery test was performed, and the tip of the tube was considered to be satisfactorily positioned if 80–100 ml of water were recovered. The gastric juice samples were collected by manual aspiration in 15-min periods. Pyloric losses and duodenogastric reflux were not estimated. The amount of acid collected was determined by titration to pH 7·0 with 0·1 M NaOH using an automatic titrator (Autoburette Radiometer, Copenhagen, Denmark). A basal period of 60 min was initially observed, but in order to empty the stomach totally and reach a basal secretory steady state only samples collected between $t = -30$ min and $t = 0$ were taken into account for the calculation of basal acid output in millimoles per hour. At the end of this period the subjects were served an appetizing meal consisting of about 100 g beef steak and 100 g fried mushrooms. Under constant supervision, they were asked to chew and spit out this meal during a 15 min period and were allowed to wash out their mouths with water to eliminate food particles that might otherwise be swallowed. Gastric juice was then collected between $t = +15$ and $t = +60$ min, and MSF-stimulated acid output in millimoles per hour was calculated from the two consecutive largest outputs. At the end of the MSF test period, pentagastrin (Peptavlon, ICI Pharmaceuticals, Macclesfield, UK) was injected subcutaneously (6 μg kg^{-1}) and the gastric juice was then collected in four 15-min samples, i.e. between $t = 60$ and $t = 120$ min Pentagastrin-stimulated acid output in millimoles per hour was calculated from the two consecutive largest outputs. Except during the 'meal' period, saliva was aspirated throughout the experiment. During all tests, gastric aspirates were carefully checked for swallowed particles: few or none were found.

Statistics

Examination of data showed that preoperative MSF-stimulated acid output, preoperative pentagastrin-stimulated acid output and postoperative pentagastrin-stimulated acid output were normally distributed, while preoperative basal acid output, postoperative basal acid output and postoperative MSF-stimulated acid output were not (*Table 1*). Therefore, as a rule, non-parametric Spearman rank correlations were calculated except for preoperative MSF-stimulated acid output, preoperative pentagastrin-stimulated acid output and postoperative pentagastrin-stimulated acid output, for which a standard program for multiple regression analysis was used.

Results (*Figure 1*)

The overall efficiency of parietal cell vagotomy was illustrated by a reduction of 98 per cent (median 4·10 *versus* 0·06 mmol h^{-1}), 54 per cent (median 29·40 *versus* 13·55 mmol h^{-1}) and 94 per cent (median 13·05 *versus* 0·80 mmol h^{-1}) in basal, pentagastrin-stimulated and MSF-stimulated acid outputs respectively.

Simple correlation (Spearman rank test) between preoperative basal, pentagastrin-stimulated and MSF-stimulated acid outputs showed that MSF-stimulated acid output was mainly and significantly correlated ($r_S = 0{\cdot}58$, $P < 0{\cdot}01$) with basal acid output. On the other hand, basal acid output was weakly correlated ($r_S = 0{\cdot}33$, $P < 0{\cdot}05$) with pentagastrin-stimulated acid output, while no relationship was found between pentagastrin-stimulated acid output and MSF-stimulated acid output ($r_S = 0{\cdot}26$, n.s.). Simple correlation between postoperative basal, pentagastrin-stimulated and MSF-stimulated acid outputs showed significant correlations

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Table 1 *Distribution of preoperative and postoperative data*

	Preoperative acid output			Postoperative acid output		
	Basal	Pentagastrin-stimulated	Modified sham-feeding-stimulated	Basal	Pentagastrin-stimulated	Modified sham-feeding-stimulated
Sample size	50	50	50	50	50	50
Average	4·68	29·64	12·74	0·64	13·94	1·96
Median	4·10	29·40	13·00	0·06	13·55	0·80
Mode	2·4	30·0	15·0	0·0	1·9	0·0
Variance	13·235	127·348	42·362	3·077	53·386	5·928
Standard deviation	3·638	11·285	6·509	1·754	7·306	2·435
Minimum	0·3	2·3	1·3	0·0	0·9	0·0
Maximum	16·6	52·4	28·2	11·4	28·6	9·5
Range	16·3	50·1	26·9	11·4	27·7	9·5
Skewness	1·40	0·08	0·20	5·14	−0·08	1·69
Kurtosis	2·168	−0·161	−0·602	30·000	−0·876	2·440

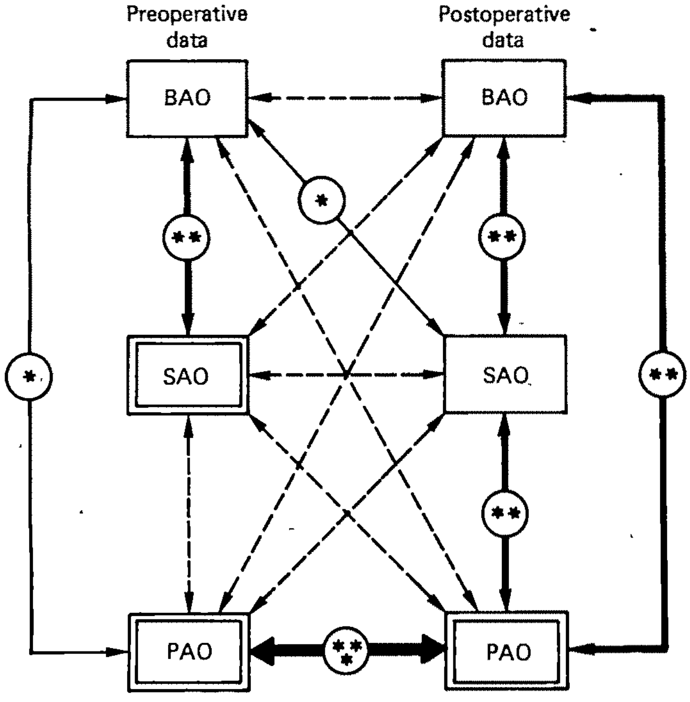

Figure 1 *Correlations between preoperative and postoperative basal acid output (BAO), modified sham-feeding-stimulated acid output (SAO) and pentagastrin-stimulated acid output (PAO).* ▭ *and* ▭, *Gaussian and non-Gaussian data distributions,* ---, *not significant,* $^*P<0·05$; $^{**}P<0·01$; $^{***}P<0·001$. *For statistical tests see text*

($P<0·01$) between basal acid output and pentagastrin-stimulated acid output ($r_S=0·43$), basal acid output and MSF-stimulated acid output ($r_S=0·49$) and MSF-stimulated acid output and pentagastrin-stimulated acid output ($r_S=0·41$). Postoperative basal acid output was not correlated with preoperative basal acid output ($r_S=0·08$, n.s.), MSF-stimulated acid output ($r_S=0·08$, n.s.) or pentagastrin-stimulated acid output ($r_S=0·14$, n.s.). Postoperative MSF-stimulated acid output was significantly correlated with preoperative basal acid output ($r_S=0·32$, $P<0·05$) but not with preoperative MSF-stimulated acid output ($r_S=0·20$, n.s.) or pentagastrin-stimulated acid output ($r_S=0·05$, n.s.). Postoperative pentagastrin-stimulated acid output was significantly correlated with preoperative pentagastrin-stimulated acid output ($r_S=0·48$, $P<0·001$) but not with basal acid output ($r_S=0·26$, n.s.) or MSF-stimulated acid output ($r_S=0·25$, n.s.). Taking into account the Gaussian distributions of preoperative MSF-stimulated acid output, preoperative pentagastrin-stimulated acid output and postoperative pentagastrin-stimulated acid output, multiple regressions were eventually calculated. They showed a significant relationship between postoperative and preoperative pentagastrin-stimulated acid output ($r_S=0·48$, $P<0·01$), which was not noticeably reinforced when preoperative MSF-stimulated acid output data were added ($r_S=0·49$).

Discussion

It is generally agreed that sham feeding is a harmless and efficient method for stimulating gastric and pancreatic vagal drive. However, it is also a cumbersome and time-consuming method, which requires the attentive participation of the patient, who must be asked not to swallow food particles. Thus the cost-efficiency ratio and therefore the usefulness of the test can be questioned when it is used in clinical practice, either to evaluate preoperative or postoperative residual 'vagal tone', or to predict or to measure postoperative acid secretory rates and thus to infer recurrence probability. Indeed, the relationship between ulcer recurrence probability and preoperative and/or postoperative acid secretory rates can be determined only by follow-up studies. Therefore the present study was not directly addressed at ulcer recurrence but was conducted to discover whether sham feeding is a useful test. In fact, authors have paid attention to criteria other than acid secretion, such as pepsin secretion[4] or plasma pancreatic polypeptide response[17]. However, in duodenal ulcer patients and healthy controls, it has not been possible to discover any correlation between pancreatic polypeptide response and acid secretory rates[7,8]. Moreover, in duodenal ulcer patients before and after parietal cell vagotomy, Forichon *et al*[9] observed that neither basal pancreatic polypeptide concentrations nor MSF-induced pancreatic polypeptide responses showed any correlation with the corresponding acid values, and they suggested that plasma pancreatic polypeptide concentrations cannot be used as an endocrine marker of the vagal impulses delivered to the oxyntic mucosa either before or after parietal cell vagotomy. Therefore it remains to focus on acid secretory parameters and to evaluate the importance of information added by the MSF test to simpler and more classical basal acid output and pentagastrin-stimulated acid output rates. Our results show that preoperative MSF-stimulated acid output is highly correlated with preoperative basal acid output, but does not display any relationship with postoperative parameters. Moreover, the addition of preoperative MSF-stimulated acid output data to preoperative pentagastrin-stimulated acid output data does not increase the close relationship of the latter with postoperative pentagastrin-stimulated acid output values. On the other hand, postoperative MSF-stimulated acid output is closely correlated with postoperative basal acid output, postoperative pentagastrin-stimulated acid output and preoperative basal acid output. Therefore, the present analysis suggests that preoperative MSF-stimulated acid output, formerly proposed as a tool to assess vagal tone[3,8,15], could be simply replaced by preoperative basal acid output. Postoperatively, it is unlikely that MSF-stimulated acid output could add any original information to that already provided by postoperative basal or pentagastrin-stimulated acid outputs and, therefore, that it could be eventually of some help in the assessment of the completeness of vagotomy or the risk of recurrence.

In conclusion, for the sake of simplicity it is suggested that the MSF test could be deleted from routine secretory gastric testing before and after parietal cell vagotomy.

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Anterior lesser curvature laser seromyotomy with posterior truncal vagotomy: a potential treatment of peptic ulcer disease

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Anterior lesser curvature seromyotomy combined with posterior truncal vagotomy has been suggested as an alternative to proximal gastric vagotomy in the treatment of peptic ulcer. The argon laser may be an ideal instrument for performing seromyotomy. This study compares anterior lesser curvature argon laser seromyotomy/posterior or truncal vagotomy with anterior proximal gastric vagotomy/posterior truncal vagotomy in a canine preparation. Six dogs underwent anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy and six others underwent anterior proximal gastric vagotomy/posterior truncal vagotomy. Gastric emptying and acid secretion studies were performed preoperatively and at 1 and 6 months postoperatively. Operating time and blood loss were determined. Anterior lesser curvature argon laser seromyotomy was performed with the argon laser at 10 W, continuous, delivered through a 600 μm unsheathed quartz fibre. Anterior proximal gastric vagotomy and posterior truncal vagotomy were performed in the standard fashion. Solid phase gastric emptying was slowed with both operations ($P<0{\cdot}05$) *but this was not manifest clinically. Blood loss (millilitres) was less following anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy than following anterior proximal gastric vagotomy/ posterior truncal vagotomy (21(6·8)* versus *95(28·1), mean (s.e.m.),* $P<0{\cdot}05$) *but operating time was not significantly different between the groups. Mean basal acid secretion was reduced by 64 per cent 6 months after anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy* ($P<0{\cdot}05$) *and by 53 per cent after anterior proximal gastric vagotomy/posterior truncal vagotomy (not significant). Mean stimulated acid secretion was reduced by 41 per cent 6 months after anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy* ($P<0{\cdot}05$) *and by 24 per cent after anterior proximal gastric vagotomy/posterior truncal vagotomy (not significant). We conclude that anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy is an acceptable alternative to anterior proximal gastric vagotomy/posterior truncal vagotomy and may provide superior parietal cell denervation with less operative blood loss.*

Keywords: Laser, peptic ulcer disease, vagotomy, seromyotomy

Proximal gastric vagotomy can be a technically demanding operation and is associated with a high rate of recurrent ulceration[1–4]. Several derivative procedures have been designed to reduce the rate of ulcer recurrence[5,6]. An operation designed to improve parietal cell denervation and decrease operating time is anterior lesser curvature seromyotomy combined with posterior truncal vagotomy. While anterior lesser curvature seromyotomy/posterior truncal vagotomy is an attractive alternative to proximal gastric vagotomy this innovative procedure has several potential disadvantages. Sharp dissection of the anterior seromuscular layer of the stomach may cause excessive blood loss and occasional mucosal perforation. An 'overlap repair' of the seromuscular incision is necessary to reinforce the stomach and to prevent reunion of vagal nerve fibres[6]. These limitations may be reduced by the use of the argon laser which creates a predictable shallow injury and is an excellent instrument for the coagulation of small blood vessels[7]

This study compares the technique and results of anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy with anterior proximal gastric vagotomy/posterior truncal vagotomy in a canine preparation

Materials and methods

Experimental design

This study was performed in three phases. In phase one the optimal argon laser dosimetry for 'safe' seromyotomy was determined Phase two was an acute, qualitative study of parietal cell denervation produced by anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy. Phase three was a chronic quantitative study in which anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy was compared with anterior proximal gastric vagotomy/posterior truncal vagotomy in 12 dogs. All dogs were cared for in accordance with the National Research Council's guide for the care and use of laboratory animals

Phase 1 laser dosimetry

Under barbiturate anaesthesia a midline celiotomy was performed in two dogs. Argon laser energy (HGM Endo-20, HGM Corporation,

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Salt Lake City, Utah, USA) was delivered through a 600 μm unsheathed quartz fibre (beam divergence 5°, spot size 2 mm). The fibre was held perpendicular, 1 cm from the gastric serosa. Linear applications were made varying the power from 2 to 15 W. The optimal laser power was defined as the minimum power necessary to divide all nerve fibres, coagulate small vessels and cause blanching of the stomach wall when the laser beam was manually moved at 1 cm/s. Multiple linear applications were then made at optimal power. Spot applications at optimal power were made at a single 2 mm spot for 1–5 s Seven days later the animals were killed and samples from each injury site were taken for histological examination.

Phase 2. acute, qualitative studies

Three 25-kg dogs underwent midline celiotomy. A long anterior gastrotomy was made and the gastric mucosa was exposed. The mucosa was neutralized with 5 per cent $NaHCO_3$ and irrigated with normal saline. Pentagastrin® (Ayerst Laboratories, New York, USA) 6 μg/kg was injected subcutaneously. One per cent congo red, an indicator dye which turns black at pH <3, was applied to the gastric mucosa and the percentage of acid secreting mucosa was estimated

Anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy was then performed: 3 cm of distal oesophagus were cleared and a posterior vagotomy was performed. The anterior vagus nerve was preserved Several large branches of the left gastric artery and vein were divided on the high lesser curvature. An unsheathed argon laser fibre (10 W, as determined in phase one) was held perpendicular, 1 cm from the gastric wall. The seromyotomy was started at the angularis incisura, 1 cm in from the lesser curvature. The laser beam was advanced along the lesser curvature at 1 cm/s, dividing all nerve fibres from the first branch of the 'crow's foot' to the cardio-oesophageal angle The congo red test was repeated.

A fourth dog underwent only anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy at initial operation. Seven days later gastrotomy and congo red assay were performed. The laser seromyotomy site was serially sectioned and examined histologically.

Phase 3 chronic quantitative studies

Twelve 25-kg mongrel dogs were subjected to a 6-month trial comparing anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy with anterior proximal gastric vagotomy/posterior truncal vagotomy. The dogs were randomized to treatment groups by tag number. Each animal served as its own control. Before operation each animal underwent solid phase gastric emptying evaluation and gastric acid secretion analysis.

Gastric emptying. Solid phase gastric emptying was assessed with a 50-g ^{99m}Tc-labelled liver meal administered after a 24-h fast. The fraction of marker remaining in the stomach was measured on completion of the meal and then every 10 min until 50 per cent of the marker had passed into the intestine. The animals were unrestrained between each 30 s γ camera acquisition period. Images were displayed on the computer screen and a region of interest was placed around the stomach. The stomach radioactivity was corrected for radioactive decay and the time to half-emptying ($t_{\frac{1}{2}}$) was calculated using linear regression curve fitting to the data[8].

Gastric acid secretion. Acid was collected by gastric aspiration[9,10]. After a 24-h fast each animal was anaesthetized with sodium pentobarbital and placed in the right lateral decubitus position. A femoral artery catheter was inserted for continuous monitoring of blood pressure. Two 14 Fr orogastric sump tubes were placed in the stomach. With fluoroscopy, the tip of one tube was positioned in the prepyloric antrum and the second tube was positioned immediately below the gastroesophageal junction Low intermittent suction (40 cmH_2O) was applied to the distal tube. Polyethylene glycol (2·5 per cent) in isotonic saline (pH adjusted to 5·0) was infused through the proximal tube at a rate of 3·3 ml/min. The stomach was lavaged with isotonic saline and all fluid was removed. Subsequently, all gastric fluid was continuously aspirated through the distal tube and collected every 15 min After 15 min of aspiration under basal conditions pentagastrin (6 μg/kg) was injected subcutaneously. Antral aspiration was continued for a further 90 min. The hydrogen ion concentration of each aliquot was determined by the glass electrode technique[11]. Polyethylene glycol concentration was assessed turbidometrically[12]. Fractional polyethylene glycol recovery and HCl secretion were calculated[10] After the first six assays it became apparent that polyethylene glycol infusion was unnecessary as there was minimal transpyloric loss of marker. Basal acid output (millimoles per hour) was the amount of acid recovered in the 15 min before pentagastrin administration multiplied by four. Stimulated acid output was the amount of acid recovered 1 hour after subcutaneous pentagastrin.

Operation. After preoperative studies and randomization, six animals underwent anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy and six underwent anterior proximal gastric vagotomy/posterior truncal vagotomy Anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy is described above. Anterior proximal gastric vagotomy was performed in a conventional fashion[2] The operative procedures were performed by a surgeon well experienced with gastric operations (J.B.) and by a senior surgical resident (J.H.). Blood loss for each procedure was determined by sponge weight.

Follow up Gastric emptying evaluation was performed 6 weeks postoperatively Basal and stimulated gastric acid secretion were measured 1 and 6 months after operation

Statistical analysis

The Wilcoxon signed rank test was used to compare results before and after operation in each animal. The Wilcoxon rank sum test was used to compare results in animals undergoing anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy with animals undergoing anterior proximal gastric vagotomy/posterior truncal vagotomy. All results are listed as mean (s.e.m.).

Results

Phase 1: laser dosimetry

Consistent neurolysis was achieved with the argon laser at 10 W, continuous wave, when the laser was advanced at a rate of 1 cm/s. This corresponds to an average energy fluence (laser dose) of 63·6 J/cm^2. This mode of application caused only partial thickness injury of the gastric wall (*Figure 1a*). Full thickness injury occurred when the argon laser at 10 W was held on one 2 mm spot for 5 s. This corresponds to an average energy fluence of 1592 J/cm^2, 25 times greater than the energy fluence needed to perform adequate seromyotomy (*Figure 1b*). No gross perforations occurred in any of these studies.

Phase 2: acute studies – qualitative assay

Before operation approximately 50 per cent of the parietal cell mass achieved pH <3·0 after pentagastrin stimulation. Following anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy the parietal cell mucosa with pH <3·0 after pentagastrin stimulation was estimated to be nil, 2 and 5 per cent in the three experimental animals. In the animal surviving 1 week after anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy <5 per cent of the parietal cell mucosa attained a surface pH <3. Acid secreting mucosa 'missed' by anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy was located on the lesser curvature at the junction of the antrum and body of the stomach.

Phase 3: chronic studies – quantitative assay

Gastric emptying. Before operation, mean (s.e.m.) solid phase gastric emptying $t_{\frac{1}{2}}$ was 69(11·3) and 53(8·2) min for the animals randomized to anterior proximal gastric vagotomy/posterior truncal vagotomy and anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy respectively (n.s.). After operation, mean $t_{\frac{1}{2}}$ was 101(20·8) and 77(10·9) min for animals undergoing anterior proximal gastric vagotomy/posterior truncal vagotomy and anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy respectively (n.s.). Solid phase gastric emptying was slowed significantly and equally by either operation ($P<0·05$). This delay was not manifest clinically as no animal developed anorexia, weight loss or vomiting after either procedure.

Gastric acid secretion. Anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy reduced basal acid output at 6 months and pentagastrin-stimulated acid output at 1 and 6 months after the operation ($P<0\cdot05$; *Table 1*). Although reductions in basal acid output and stimulated acid output were seen after anterior proximal gastric vagotomy/posterior truncal vagotomy, they did not reach statistical significance.

Operation. The mean (s.e.m.) operative time for anterior lesser curvature argon laser seromyotomy was 20·7(1·6) min and for anterior proximal gastric vagotomy was 27·2(3·2) min (n.s.). The mean operative blood loss for anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy was 21·0(6·8) ml and for anterior proximal gastric vagotomy/posterior truncal vagotomy was 95·0(28·1) ml ($P<0\cdot05$). There were no complications resulting from surgery in either group.

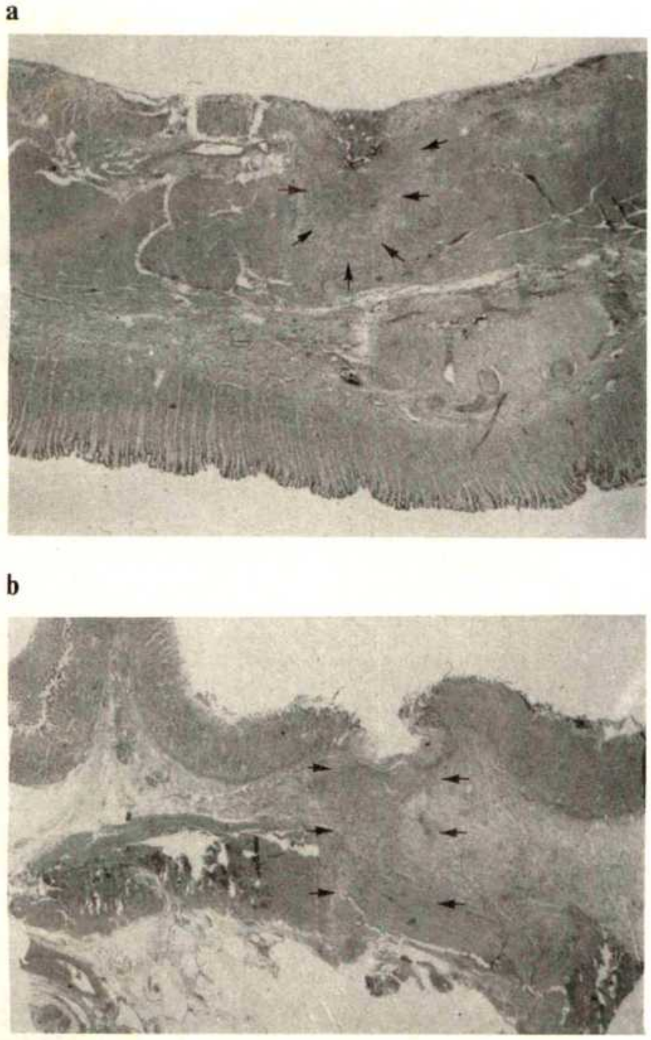

Figure 1 *Gastric wall injury 7 days after argon laser serosal application:* **a** *with argon 10 W continuous wave advanced at 1 cm/s (energy fluence 63·6 J/cm^2) a partial thickness injury was produced (arrows);* **b** *full thickness injury occurred (arrows) when the argon laser at 10 W was held in one spot for 5 s (energy fluence 1592 J/cm^2)*

Discussion

Anterior lesser curvature seromyotomy/posterior truncal vagotomy, first described in 1982[6], has recently been compared with proximal gastric vagotomy in a prospective randomized trial of 91 patients followed for a median of 3 years[13]. Postoperative complications, postoperative peak acid output, patient satisfaction and ulcer recurrence rates were the same after both procedures. Anterior lesser curvature seromyotomy/posterior truncal vagotomy was performed in a shorter time with fewer difficulties than proximal gastric vagotomy.

In this animal study we have demonstrated that anterior lesser curvature seromyotomy/posterior truncal vagotomy performed with an argon laser produces superior acid reduction to anterior proximal gastric vagotomy/posterior truncal vagotomy. While the finding that anterior proximal gastric vagotomy/and posterior truncal vagotomy produced no significant reduction in acid output may have resulted from a small sample size, it appears that anterior lesser curvature argon laser seromyotomy provided greater parietal cell denervation than anterior proximal gastric vagotomy. Possible mechanisms for superior denervation with anterior lesser curvature argon laser seromyotomy are: (1) severed nerve fibres may have regrown to a greater extent following anterior proximal gastric vagotomy than following anterior lesser curvature argon laser seromyotomy; (2) nerve fibres and ganglion cells in the myenteric plexus of the stomach are destroyed with anterior lesser curvature argon laser seromyotomy as this layer is within the penetration depth of the argon laser. Destruction of these intramural neurons may provide more complete parietal cell denervation after anterior lesser curvature argon laser seromyotomy than occurs after anterior proximal gastric vagotomy; (3) small vagal branches may have been missed with anterior proximal gastric vagotomy but not with anterior lesser curvature argon laser seromyotomy, a plausible explanation given the simplicity of anterior lesser curvature argon laser seromyotomy.

Reduction in acid secretion following anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy in our canine model is similar to that reported in clinical series of anterior lesser curvature seromyotomy/posterior truncal vagotomy. In one series of 29 patients undergoing anterior lesser curvature seromyotomy/posterior truncal vagotomy, 6 month postoperative basal acid output and stimulated acid output were reduced to 60 per cent and 40 per cent of preoperative values respectively[14]. At 6 months our values for basal acid output and stimulated acid output reduction following anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy were very similar at 64 and

Table 1 *Basal and stimulated acid secretion following anterior lesser curvature laser seromyotomy with posterior truncal vagotomy and following anterior proximal gastric vagotomy with posterior truncal vagotomy*

	Basal acid output (mmol/h)			Stimulated acid output (mmol/h)		
	Preoperative	Postoperative		Preoperative	Postoperative	
		1 month	6 months		1 month	6 months
Anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy	3·9(0·73)	4·4(0·80)	1·4(0·93)*	34·1(5·2)	19·5(4·6)*	20·2(5·1)*
Anterior proximal gastric vagotomy/posterior truncal vagotomy	7·2(1·9)	5·4(1·4)	3·4(1·2)	32·0(4·0)	18·1(3·8)	24·3(2·9)

All values are mean and s.e.m.; *$P<0\cdot05$ when compared with preoperative acid output (Wilcoxon rank sum test)

41 per cent respectively. The method of gastric acid secretion analysis was identical in both studies.

Solid phase gastric emptying, as determined by radionuclide scintigraphy, was delayed after both anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy and anterior proximal gastric vagotomy/posterior truncal vagotomy. It has been well shown in canine studies[15] and several clinical series that preservation of a single nerve of Latarjet is sufficient to maintain normal gastric emptying[6,13,14,16–18]. Unlikely explanations for delayed gastric emptying are consistent inadvertent anterior vagus nerve injury or persistent postoperative gastric ileus. Despite radiological evidence of delayed gastric emptying none of the experimental animals developed clinical evidence of gastric stasis.

Anterior lesser curvature seromyotomy/posterior truncal vagotomy has rarely produced gastric stasis in humans. In a co-operative series of 605 patients undergoing anterior lesser curvature seromyotomy/posterior truncal vagotomy, 1·7 per cent developed symptomatic gastric stasis, a drainage procedure was required in 1·3 per cent and 0·33 per cent developed diarrhoea[16]. Solid phase gastric emptying studies performed after anterior lesser curvature seromyotomy/posterior truncal vagotomy have shown no delay in emptying with this procedure.

The major advantages of lesser curvature seromyotomy over parietal cell vagotomy are speed and safety. In our study, the mean time required to perform anterior lesser curvature argon laser seromyotomy was 25 per cent less with that required to perform anterior proximal gastric vagotomy, a speed advantage commented on in most clinical series of anterior lesser curvature seromyotomy/posterior truncal vagotomy[13,14,17]. The risk of injuring the nerve of Laterjet is less with anterior lesser curvature seromyotomy/posterior truncal vagotomy than with proximal gastric vagotomy because the seromyotomy incision occurs 2·5 cm away from the nerve[6]. While no perforations have occurred with anterior lesser curvature seromyotomy/ posterior truncal vagotomy, ischaemic necrosis of the lesser curvature is a known complication of proximal gastric vagotomy. A recent investigation of lesser curvature blood flow after proximal gastric vagotomy found an average decrease in mucosal blood flow of 57 per cent and many areas were found where the mucosal blood flow had been critically diminished[19].

If anterior lesser curvature seromyotomy/posterior truncal vagotomy is technically easy, is associated with only rare complications and provides results as good as proximal gastric vagotomy, what advantages can the argon laser possibly confer? The theoretical attractions of anterior lesser curvature argon laser seromyotomy are haemostasis, speed and safety. The mean blood loss following anterior lesser curvature argon laser seromyotomy/posterior truncal vagotomy in this study was 22 per cent of the blood loss following anterior proximal gastric vagotomy/posterior truncal vagotomy. Laser seromyotomy results in diminished blood loss because small vessels are coagulated as they are cut with the laser. Laser seromyotomy may be performed more rapidly than sharp seromyotomy because there is no need to reinforce the seromyotomy incision with an 'overlap repair'. While inadvertent mucosal laceration occasionally occurs with sharp dissection, it is nearly impossible to create a transmural gastric injury with the argon laser. In a worst case analysis, transmural necrosis with the argon laser required an energy fluence 25 times that necessary for seromyotomy. Even at this energy level gross perforation did not occur. While these factors provide a conceptual advantage to laser use, it will be necessary to compare laser with sharp seromyotomy under well controlled conditions before claiming the superiority of argon laser seromyotomy over conventional seromyotomy.

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Early prediction of late incisional hernias

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Incisional (ventral) hernias may not be discovered until many months after operation[1,2]. This has led to the belief that aponeuroses that have healed edge to edge may gradually part and permit the development of a hernia[2]. An alternative hypothesis is that a gap forms between the edges of the divided aponeurosis soon after operation, and that the weak fibrous tissue filling that gap gradually stretches until a hernia becomes detectable. The present study was carried out to test the validity of this hypothesis.

Patients and methods

After 163 major laparotomies, pairs of stainless steel haemostatic clips (Ligaclips®, Ethicon Ltd., Edinburgh, UK) were attached opposite each other to the edges of the sutured aponeurosis before closure of the skin. All patients were seen in the outpatient department about 1 month later and agreed to have abdominal radiographs taken, the purpose having been explained to them. The radiographs were taken postero-anteriorly, and the separation between pairs of clips was measured.

Patients were followed up at intervals. Herniation was diagnosed if a bulge appeared when the patient stood and coughed and a defect could be felt in the aponeurosis. The examining surgeon had no knowledge of the results of the radiographs taken at 1 month; these measurements were recorded on the research forms, not in the case notes. The presence or absence of an incisional hernia was checked at later follow-up examinations.

Of the 163 patients, 14 were withdrawn: in six several of the clips had fallen out because of wound infections and the radiographs at 1 month could not be assessed; five patients died within 6 months of operation; one incision was reopened within 6 months; two were lost to follow-up after the 1-month visit.

Results

The details of the remaining 149 patients are shown in *Table 1*. Radiographs from 131 patients showed minimal separation (less than 12 mm) between opposing pairs of clips, and only one patient developed an incisional hernia. She was a thin woman aged 80 years who had had a resection of the left colon for cancer through a lower midline incision that was closed with a continuous mass nylon suture. Radiographs at 1 month showed no separation of the clips, and 6 months after operation there was no sign of an incisional hernia. At 12 months, however, a bulge was seen beneath the upper half of the scar. Two years after the operation she had no complaints and was discharged. The remaining 130 patients in this group were followed up for between 6 and 75 months (median 25 months), and none showed clinical signs of incisional herniation.

There were 18 patients whose radiographs at 1 month showed separation of pairs of clips of 12 mm or more (median 40 mm, range 12–70 mm). One woman (aged 79 years at the time of operation) was reported by her general practitioner to have no incisional hernia 29 months after repair of a perforated duodenal ulcer through a midline incision that was closed with a continuous mass nylon suture; the radiograph at 1 month had shown separation of the upper two of three pairs of clips of 33 and 40 mm, the lowest pair being together.

Table 1 *Details of 149 patients*

	Total number of patients	Clips separated ($n = 18$) No. (%)	Clips separated ($n = 18$) 95% Confidence interval
Men	59	9 (15)	7·2 to 27·0
Women	90	9 (10)	4·6 to 18·2
Age (years)			
<40	23	1 (4)	0 to 22·5
40–69	76	10 (13)	6·4 to 22·9
≥70	50	7 (14)	5·7 to 26·9
Type of incision			
Midline	117	16 (14)	8·0 to 21·3
Paramedian	11	1 (9)	0 to 42·2
Lateral paramedian	8	0	
Transverse	13	1 (8)	0 to 36·9
Through previous incision	4	1 (25)	0 to 82·4
Site of incision			
Upper	84	7 (8)	3·4 to 16·5
Middle	19	3 (16)	3·1 to 40·0
Lower	46	8 (17)	7·7 to 31·5
Thickness of subcutaneous fat			
<25 mm	91	8 (9)	3·8 to 16·7
≥25 mm	58	10 (17)	8·5 to 29·5
Wound closure			
Mass (nylon)	130	17 (13)	7·8 to 20·1
Layered (Dexon®/nylon)	19	1 (5)	0 to 26·7
Operation			
Emergency or urgent	67	17 (25)	15·5 to 37·5
Elective	82	1 (1)	0 to 6·8
Surgeon			
Consultant	66	10 (15)	7·5 to 26·2
Registrar	83	8 (10)	4·2 to 18·2
Disease			
Malignant	35	4 (11)	3·1 to 27·0
Benign	114	14 (12)	6·9 to 19·8
Wound discharge			
Present	33	13 (39)	22·8 to 58·0
Absent	116	5 (4)	1·4 to 9·8

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The remaining 17 patients all developed hernias. One required repair and one a supporting belt; the rest had no symptoms. Eight of these hernias were discovered within 6 months of operation, three more at a year, and the remaining six at 16, 24, 28, 29, 36, and 43 months.

Discussion

This study is an extension and long-term follow-up of the pilot study published in 1986[3]. We found only one exception to the rule that wide separation of the anterior aponeurosis within a month of laparotomy predicts the subsequent development of an incisional hernia, and one exception to the rule that patients whose aponeuroses have healed in close apposition do not subsequently develop hernias.

Several variables were associated with higher rates of early separation of the aponeurotic suture line and subsequent herniation. Significant in the present study were emergency or urgent operations, and postoperative wound discharges (in both cases Fisher's exact probability = 0·001). The higher incidences of aponeurotic separation in midline incisions compared with paramedian, lateral paramedian, and transverse incisions, and in those sutured *en masse* rather than in layers, were not significant, but the type II error is obvious. Significantly lower rates of herniation in paramedian and lateral paramedian incisions have been reported[4,5].

Perhaps we should have arranged radiographs for our patients sooner than 1 month after operation—it may be that

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separation of the aponeuroses occurs within the first few days. This is a question yet to be answered.

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Combination chemotherapy is more effective in postspillage prophylaxis for hydatid disease than either albendazole or praziquantel alone

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Recurrence is one of the most significant postoperative complications following surgery in man for *Echinococcus granulosus*, occurring in approximately 10 per cent of patients[1]. When recurrence occurs, further surgery is associated with increasing morbidity and mortality[2]. It has previously been reported that a short course of oral albendazole after spillage of viable protoscolices can significantly reduce the risks of cyst development in a gerbil model[3] and that the timing of albendazole prophylaxis to spillage was of great importance[4]: it was ineffective when given 15 days later. The isoquinoline praziquantel has been found to be a more effective scolicidal agent in *in vitro* cultures of *E. granulosus*[4]. We have previously shown that combinations of albendazole and praziquantel are more effective than either agent alone in *in vitro* culture[5]. In this paper we study *in vivo* results in an animal model of peritoneal spillage.

Materials and methods

Thirty-nine gerbils were each injected intraperitoneally with approximately 4000 viable protoscolices obtained from viable ovine cysts of *E. granulosus*. The gerbils were divided into a control and three treatment groups: ten received a 1-month course of albendazole (50 mg kg^{-1} day^{-1}), ten received a 1-month course of praziquantel (500 mg kg^{-1} day^{-1}) and ten gerbils received 1 month of a combination of praziquantel (500 mg kg^{-1} day^{-1}) and albendazole (50 mg kg^{-1} day^{-1}). All drugs were given by once daily gavage starting within 24 h of intraperitoneal infection. The remaining nine animals became the infected untreated controls. Eight months after inoculation, the gerbils were killed. The number of cysts in each animal in each group was measured at necropsy. The Mann–Whitney U test was used.

Results

All the gerbils survived until the end of the experiment. It was found that the number of cysts developing in any of the three test groups (albendazole treated mean (s.d.) 22·6(10·0) cysts per gerbil, praziquantel treated 5·9(1·09) and combination treated 0·8(0·29)) was significantly less ($P<0{\cdot}01$) than the number developing in the controls (67·6(12·8) cysts per gerbil). It was also found that a combination of the two drugs was significantly more effective ($P<0{\cdot}001$) than when either drug was given alone. Praziquantel alone showed a trend to more effective reduction of the number of cysts at this particular dosing regimen, compared with albendazole ($P<0{\cdot}1$).

Discussion

We have previously shown that even 7 days treatment with albendazole after intraperitoneal inoculation of protoscolices of *E. granulosus* in a gerbil model host can reduce the number of cysts that develop.

In vitro culture of protoscolices has shown their sensitivity to the isoquinoline praziquantel[6,7]. We have also defined the minimum concentrations and time of drug exposure[8,9]. Praziquantel is an active scolicidal agent at concentrations as low as 20 μg litre^{-1} (compared with 250 μg litre^{-1} of albendazole sulphoxide) and exposure time can be as low as 30 min at a high concentration[10]. Albendazole does however have a proven effect on the germinal layer of the parasite[11], and this drug may be useful in the postoperative patient where tiny undetected cysts may remain. This study clearly demonstrates that combined chemotherapy with albendazole and praziquantel in an animal model is more effective than either agent when given alone, and should be considered in clinical practice.

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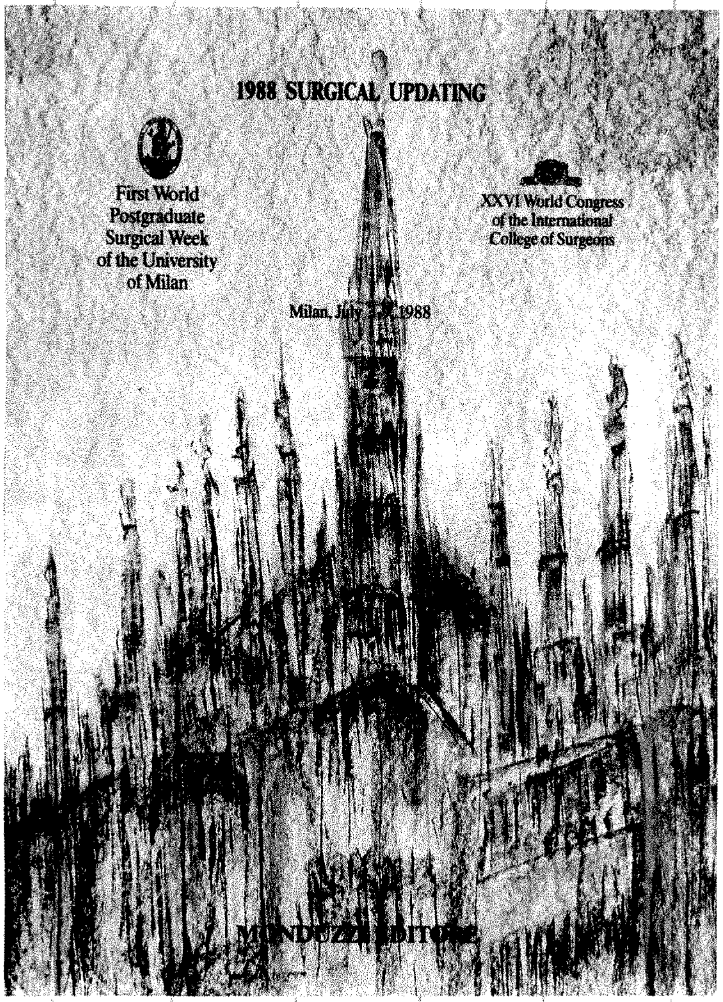
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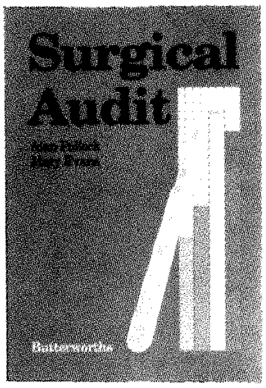

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Br. J. Surg. 1989, Vol. 76, September, 955–957

Conservative treatment of ingrowing toenails

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A combination of conservative measures was used to treat 105 patients with 119 ingrowing toenails. The method proved to be simple and cheap, but time consuming. Post-treatment discomfort and the time taken to return to normal activities were acceptable; the cosmetic result was good. Two-year follow-up revealed that the success rate of the method in less advanced cases (stages I and II) was high (96 per cent), although in the long term there was a tendency to recurrence in stage II cases. The failure rate in advanced cases (stage III) was high (up to 62 per cent). Conservative treatment can be used successfully in mild cases of ingrowing toenails.

Keywords: Ingrowing toenails, conservative treatment

Ingrowing or, more accurately, embedded toenails are a common cause of pain and discomfort and can occur in any person of any age but are most common in male adolescents. There is little uniformity in treatment as the method should satisfy several criteria· the procedure should be simple and cheap, there should be little post-treatment discomfort, return to normal activities should be quick, the percentage of complications should be low, the recurrence rate should be minimal and the resulting toe should be cosmetically acceptable

Several surgical procedures and chemical ablation of the nail matrix have been described, and well documented studies have been reported[1–5]. Conservative treatment is frequently associated with a high recurrence rate and a high percentage of defaulters[6]. However, conservative treatment of the ingrowing toenail can succeed, even in advanced cases[7], but reports of such treatment are rare.

We have studied a combination of conservative measures in the light of the above criteria.

Patients and methods

A prospective study was performed, according to a fixed protocol, on 105 consecutive patients with ingrowing toenails. The patients were treated by one of a group of ten general practitioners or on an out-patient basis by one of the authors (J A M.R.). Only patients with ingrowing nails of the big toe were included in the study. Patients with onychogryphosis, onychomycosis and obvious orthopaedic foot disorders, such as hallux valgus and hammer toes were excluded from the study.

After diagnosis and obtaining informed consent the toe was cleansed. Any spur of the nail edge was removed. The middle one-third of the nail (10–15 mm) was thinned by filing the upper surface until the matrix beneath it could be seen. The offending nail edge was lifted out of the nail fold and debris was removed from under it. Granulation tissue was reduced by silver nitrate application. A small piece of cotton wool, soaked in alcohol 60 per cent, was packed firmly under the nail edge (*Figure 1*). The patients were instructed to renew the cotton wool once a day They were also given advice on footwear and foot hygiene, especially nail trimming They were told to resume normal activities as soon as possible

The patients were asked to return for assessment after 2 weeks. Any residual granulation tissue was treated with silver nitrate. If signs of inflammation were still present the patients were instructed to continue packing They were told to restart packing if the symptoms and signs of inflammation returned All patients were asked to note the first day on which they had no more symptoms and the day on which they resumed normal activities. They were asked to file the nail shortly before each check visit. All patients were seen by one person (J A.M.R) at 1, 12 and 24 months after presentation to assess correct nail filing and symptoms and signs of recurrence. At 4 and 8 months they were seen by their general practitioner or by J.A.M R. Indications for abandoning the conservative approach were persistent disabling pain, the development of cellulitis, and by request of the patient.

Patients were divided into three groups, according to the stage of ingrowing toenail at presentation. For this purpose the stages described by Heifetz[8] and Mogensen[9] were used The first stage is characterized by pain, reddening and slight swelling of the nail wall. In the second stage, swelling, pain and redness are accompanied by infection and suppuration. In the third stage, formation of granulation tissue and hypertrophy of the nail wall occur and all characteristics of the second stage are more markedly present. Patients were considered cured at the time they had no symptoms and no signs of inflammation

Results

We treated 105 patients, 65 male patients and 40 female patients. The mean age at presentation was 21·9 years (range 12–79 years); 78 per cent were under 30 years old Both feet were simultaneously affected in 14 patients. The lateral side of the nail was involved in 65 cases, and the medial side in 35 cases. In the remaining cases, both sides were affected. As regards cause, a history of improper nail trimming was identified in 82 cases, injury to the toe in 65 cases, tight footwear in 40 cases, and hyperhidrosis in 67 cases Hyperhidrosis almost always occurred in combination with the wearing of tight synthetic socks. Fourteen patients had been previously treated by nail avulsion and 16 by wedge resection; 23 patients had been treated by a chiropodist.

Twenty patients presented with stage I ingrowing toenails, 47 with stage II and 52 with stage III Sex and age were similarly distributed between the three groups. The mean duration of symptoms was 9 weeks for stage I, 11 weeks for stage II and almost 14 weeks for stage III The distribution of all cases over the three stages, cured cases and cases which were treated

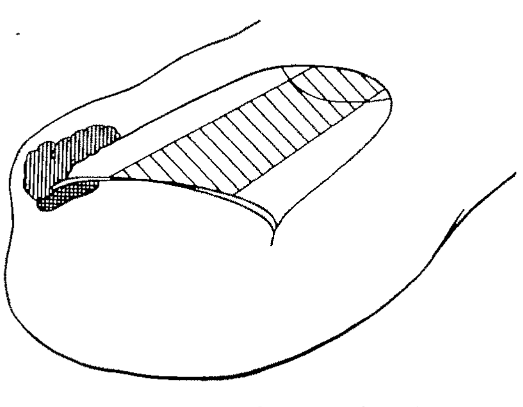

Figure 1 *Ingrowing toenail treated by filing the nail, packing the nail fold and reducing granulation tissue by the application of silver nitrate*

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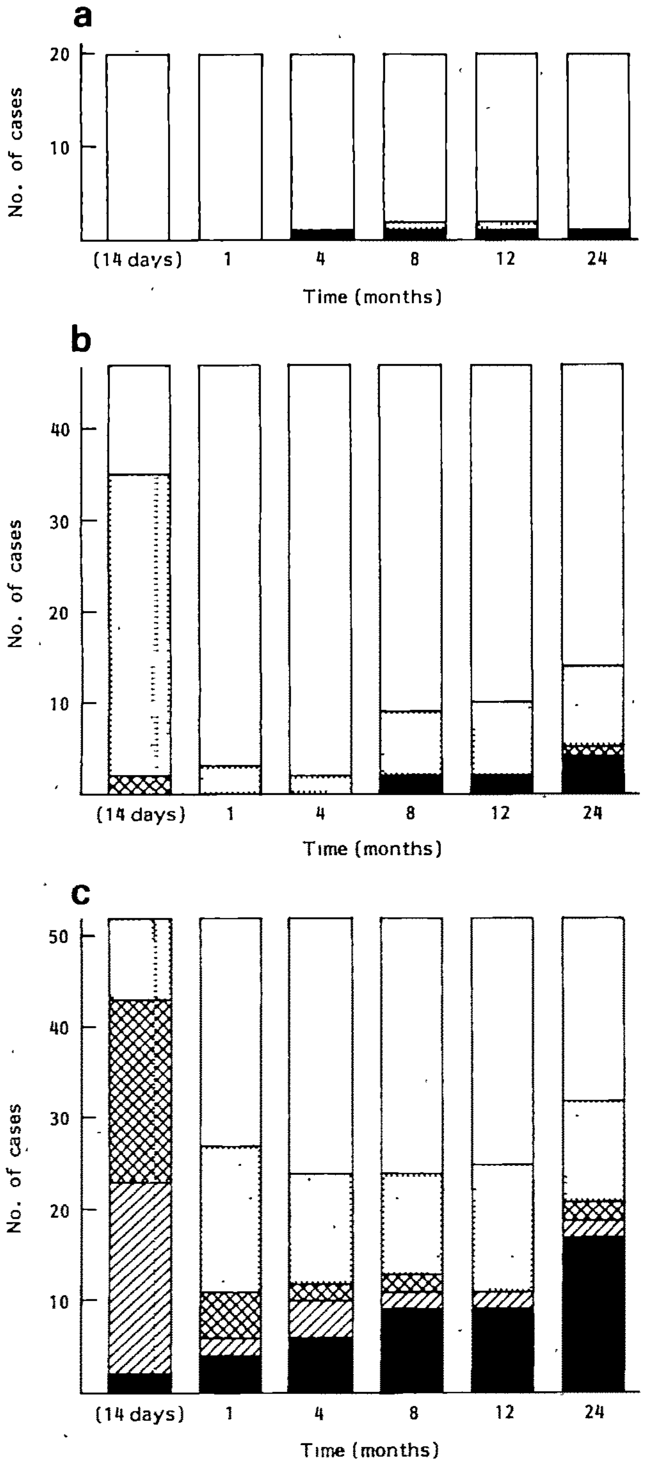

Figure 2 *Outcome at different intervals after presentation in* **a** *20 cases with stage I,* **b** *47 cases with stage II and* **c** *52 cases with stage III ingrowing toenails* □, *cured,* ▨, *stage I,* ▩, *stage II,* ■ *stage III,* ■, *surgical treatment*

surgically at different intervals after presentation, is shown in *Figure 2*.

Of the cases presenting in stage I, all were cured within 14 days. In only two did symptoms and signs of stage I ingrowing toenails recur and these patients were treated successfully with the same regimen. One patient, initially presenting in stage I, had complaints 2 months after presentation without any sign of inflammation. She insisted on surgical treatment. After segmental matrix excision and phenolization, she complained of the cosmetic result, but had no pain.

The cases with stage II ingrowing toenails were, for the greater part (44 cases), cured within 4 months but, between 4 and 24 months, symptoms and signs recurred in 18 cases, of which only four were treated successfully with conservative measures.

About one-half of the patients with stage III ingrowing toenails continued to complain and, as a result, 12 asked for surgical treatment. In contrast, two patients with stage III (nail wall hypertrophy) did not improve for 24 months but refused surgical therapy. Of the 28 patients with stage III who were cured after 4 months, nine developed symptoms and signs which could be treated conservatively in only one case. Two stage III patients had to be treated surgically within 2 weeks from presentation because of cellulitis. Nine of 30 cases treated surgically in the past presented with stage II; of these seven could be cured, but in four cases there was a recurrence. Of the other 21 cases only two could be temporarily cured.

Table 1 shows the pain duration and the time taken to return to normal activities for those patients in each group who were cured. Only 15 patients (11 women) had complaints with regard to the cosmetic result Most men did not seem to care very much and women used nail varnish as camouflage An inconvenience was rupture of the nail so that socks could easily get snagged. This happened 31 times.

At 53 of all check visits, patients had to be reinstructed because they had not filed the nail correctly. Packing the nail fold was never a problem.

We calculated that the cost of materials, such as files, cotton wool, and alcohol, was less than 5 pounds sterling. For stage I ingrowing toenails, two or three check visits were necessary. For stage II patients, at least three visits were required. Half the patients with stage III lesions had to be seen at least six times.

Discussion

In the past, nail avulsion, wedge resection, total matrix ablation and other surgical treatments of ingrowing toenails have been associated with high recurrence rates, considerable postoperative pain and poor cosmetic results[1,2]. More recent studies have shown that, with segmental matrix excision, segmental phenolization, and wedge resection in combination with segmental phenolization, far more acceptable results can be achieved[3–5]. For the results of conservative treatment, most authors have referred to the article by Lloyd-Davies and Brill published in 1963[6]. These authors treated 100 consecutive patients in their toe clinic by warm soaks, cotton wool packing beneath the nail and in nail grooves, removing granulations by silver nitrate application, and extensive hygiene instruction. Some of their patients had been treated previously by total nail avulsion. According to their article, 33 per cent of patients were discharged cured after 2 years, and 27 per cent were still under treatment. Forty per cent had defaulted[6]. However, a success rate of 79 per cent for conservative management has been reported even in advanced cases, although follow-up has only amounted to 6 months[7]

Our study shows that conservative treatment of ingrowing toenails is simple but time consuming. It requires a high degree of co-operation from the patient and perseverance on the part of the doctor. Because of the intensive support necessary it is not a cheap method of treatment. The cosmetic result, post-treatment pain duration and time taken to return to normal

Table 1 *Mean postoperative pain duration and mean time taken to return to normal activities in 93 cases of successfully treated ingrowing toenail*

Stage	No of patients cured	Pain duration (days)	Time to resumption of normal activities (days)
I	20	2	1
II	45	5	5
III	28	17	15

activities are acceptable For stage I ingrowing toenails the combination of conservative measures studied was shown to be successful. In cases of stage II ingrowing nails, success can also be achieved but recurrences are frequent in the long term (30 per cent). The failure rate is much higher in advanced cases (62 per cent in stage III), especially in patients who have previously been treated surgically. These patients can only be cured at the cost of great effort on the part of both patient and doctor. However, conservative treatment must be considered before proceeding to surgery for patients with stage III ingrowing toenails who suffer from vascular disease or diabetes.

We conclude from our data that stage I ingrowing toenails can be successfully treated by packing the nail fold with cotton wool after thinning the nail. Cure of stage II lesions can only be achieved by these measures if co-operation from the patient is guaranteed. In stage III, a non-conservative approach seems to be indicated.

Acknowledgements

We are grateful to all participating general practitioners for their co-operation

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Short note

Br. J. Surg. 1989, Vol. 76, September, 957–958

Intraoperative colonic irrigation in the treatment of acute sigmoid volvulus

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The surgical treatment of acute left colonic obstruction continues to be a controversial subject[1]. Since the introduction of intraoperative colonic irrigation[2], resection and primary analstomosis has become an acceptable method in the treatment of obstructing carcinoma of the left colon[3].

Acute volvulus of the sigmoid colon is a rare cause of intestinal obstruction in western countries, seen mostly in mental institutions and in the very elderly, and accounting for only 3–5 per cent of all cases of mechanical obstruction[4–6]. In Turkey, particularly in the south-east region, cases of sigmoid colon volvulus are seen much more frequently and cause 25 per cent of all cases of intestinal obstruction and the majority of cases of left colon obstruction treated in our department.

The purpose of this study was to determine whether intraoperative colonic irrigation could be used in the definitive, one-stage surgical treatment of acute sigmoid volvulus by reducing the incidence of anastomotic disruption after emergency colonic resection with primary anastomosis.

Patients and methods

During the 1-year period between December 1987 and December 1988, 11 patients with acute sigmoid volvulus were admitted to our department and offered surgical treatment. Two patients refused and were managed by sigmoidoscopic reduction. These patients were later discharged without consenting to further therapy

The remaining nine patients were managed by intraoperative colonic irrigation, sigmoid resection and primary anastomosis covered by a tube caecostomy.

The patients ranged in age from 26 to 85 years with a mean age of 57 years All were men and none had a previous history of mental disease. Three patients had experienced acute sigmoid volvulus previously, and one patient had had sigmoidoscopic reduction six times. Duration of symptoms was 1–7 days with a mean (s.d.) of 3·2(2·2) days. All patients complained of cessation of defaecation, seven had abdominal pain, and three had nausea and vomiting Physical examination revealed abdominal distension in all patients. Two patients with muscle guarding proved to have a gangrenous sigmoid colon at laparotomy.

Plain abdominal radiographs obtained in all patients showed evidence of sigmoid volvulus. Routine biochemical studies were carried out. The plasma total protein level, determined in seven patients, was found to be uniformly decreased with a mean (s.d.) value of 4·9(0·8) g/dl

A left paramedian or transverse incision was used in all cases The colon was manually untwisted while care was taken not to allow faecal material to enter the empty colon distal to the volvulus The distal margin of the resection was determined and the colon was divided between two clamps

The mesocolon was clamped and resected close to the colon, and the sigmoid colon was brought out through the laparotomy wound. A 20–22 Fr gauge Foley catheter was inserted into the caecum either through a caecostomy or the appendix stump after a purse-string suture had been applied The colon was rapidly washed out with 3–5 litres of warm saline until the effluvium was clear. A three-lumen Foley catheter (*Figure 1*) used in the last four cases afforded a higher flow rate and the irrigation time was shortened.

The sigmoid colon was then divided proximally, completing the resection A two-layer colocolic primary anastomosis was performed The irrigating catheter was brought out through a separate right lower stab wound as a tube caecostomy (*Figure 2*). After an additional purse-string suture had been placed, the caecum was secured to the peritoneum with four seromuscular sutures.

Anal dilatation was routinely employed while the patient was still under anaesthesia, and a rectal tube was inserted (*Figure 2*).

The tube caecostomy was irrigated during the first 7 days to avoid plugging and was clamped 7–11 days after operation The catheter was removed in the ward 24–48 h later

Results

No mechanical problems involving the tube caecostomy were observed; 100–500 ml of fluid were drained each day

Three patients had a total of four postoperative complications. One wound infection and two wound dehiscences were

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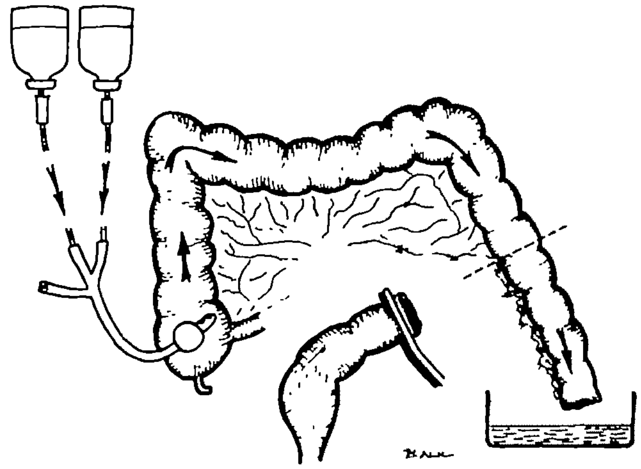

Figure 1 *The colon is washed out after the distal section has been transected. The dotted line shows the proximal margin of the resection*

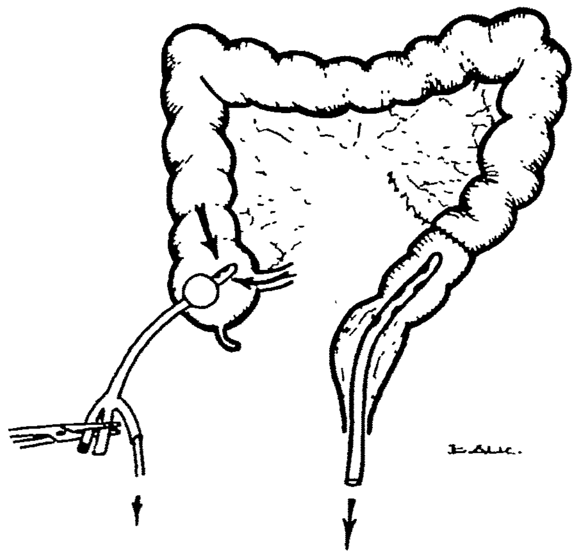

Figure 2 *After the resection the irrigating catheter is converted to a tube caecostomy and a rectal tube is placed*

observed. An anastomotic leak developed in one of the patients with wound dehiscence and was managed conservatively. This patient was later discharged with a low-grade intermittent faecal fistula (1–2 ml per day) having refused further surgical treatment.

There was no operative mortality.

Discussion

A dilemma is encountered when planning the emergency surgical treatment of acute sigmoid volvulus.

Simple operative untwisting, whether accompanied by additional fixation techniques such as sigmoidopexy or not, affords only temporary relief and is associated with a high recurrence rate[7,8] unless followed by definitive surgical treatment entailing a second operation. Resection and anastomosis, while achieving complete cure, is associated with prohibitively high morbidity and mortality rates arising from operating on an unprepared colon in the emergency setting[7,8]. Resection and end-colostomy or primary anastomosis with a proximal colostomy may be safe alternatives[6] but a further operation, with its attendant risks, for the closure of the colostomy is mandatory.

Non-operative therapy consisting of sigmoidoscopic reduction may seem to be the ideal initial treatment, relieving the obstruction and allowing the colon to be prepared for safe elective resection. While high success rates have been reported, recurrences are common[5–7,9]. Another drawback that we encountered was the unwillingness of patients, relieved of their symptoms, to undergo elective surgery. Even though the high risk of recurrence is stressed most patients refuse surgery, later returning to start the whole process again. Furthermore non-operative treatment is impossible in the presence of gangrene and may even increase the risk of perforation.

Intraoperative colonic irrigation followed by resection and primary anastomosis with the irrigating catheter converted to a caecostomy affords satisfactory surgical treatment in acute sigmoid volvulus. It achieves complete cure in one stage and no further treatment is required. This technique can be used in all cases of sigmoid volvulus. The presence of gangrene does not require any modification.

The only serious morbidity associated with this procedure was in the patient with a low volume faecal fistula. The poor general and nutritional status of our patients, as evidenced by the low plasma protein levels, may have contributed to this complication and to the two wound dehiscences. We believe that the presence of a caecostomy acting as a proximal covering colostomy prevented the development of more serious complications.

Double-lumen Foley catheters, in addition to speeding up colonic irrigation, allowed one lumen to be used for irrigation and the other for drainage during the postoperative period, preventing the formation of plugs within the caecostomy tube.

We conclude that this technique may be used in patients suspected of having a gangrenous colon and in those in whom sigmoidoscopic untwisting fails. Patients with multiple episodes of volvulus may also be considered However, sigmoidoscopic reduction followed by elective resection is still the treatment of choice when possible.

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Results of external sphincter repair in Crohn's disease

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The results of anal sphincter repair in a group of six patients with anorectal Crohn's disease are reported. All patients had previously undergone anal surgery which was followed by faecal incontinence in five. The sixth patient became incontinent following obstetric injury. Of the six patients, five are completely continent and one has a permanent stoma (follow-up from 18 months to 16 years, mean 7·8 years). Anal sphincter repair in this highly selected group of patients with Crohn's disease has not been complicated by wound breakdown or fistula formation, and has given good results.

Keywords: Crohn's disease, anus, faecal incontinence

Despite a conservative approach to the surgical treatment of perianal disease[1,2] patients with Crohn's disease are susceptible to anal sphincter damage as a result of perianal sepsis and the consequences of fistula surgery. Many patients can cope with a weak sphincter provided the colon and ileocaecal valve are preserved and their stools are formed, but should they suffer diarrhoea then incontinence is almost inevitable. Relative incontinence can be an indication for a more radical procedure on account of the concern over incontinence with a conservative operation.

Sphincter repair normally gives good results. For example, Motson[3] found in Sir Alan Parks' series that 78 per cent of patients achieved a Grade 1 result (continent of solid and liquid stool) and in a postal survey he found that nine other centres had achieved similar results. Other authors[4,5] have reported comparable success.

The fear of failure has made surgeons reluctant to consider sphincter repair in Crohn's disease[6]. In order to assess whether sphincter repair in Crohn's disease is practicable, seven patients have been assessed retrospectively.

Patients and methods

Between October 1971 and June 1986 seven patients with Crohn's disease underwent sphincter repair at St. Mark's Hospital. Of these, one patient was lost to follow-up 6 months postoperatively and has therefore been excluded from the study (*Table 1*). During the same period a proctectomy or proctocolectomy for Crohn's disease was performed in 152 patients. Anal lesions were the main indication for surgery in 35 (23 per cent) patients and a contributing factor in 66 (43 per cent), whereas in 51 (34 per cent) patients anal disease was not an indication for surgery.

All six patients had undergone previous perianal surgery, three for abscess and three for fistula. In five of the six patients the previous perianal surgery had caused the sphincter injury and consequent incontinence. The other patient had excision of oedematous skin tags following which continence was normal. Seven years later she suffered an obstetric injury and became faecally incontinent.

The time interval between the original diagnosis of Crohn's disease and sphincter repair in five patients ranged from 6 months to 8 years, while in one patient from abroad this time interval could not be ascertained.

All five women had been diagnosed histologically as having intestinal Crohn's disease: four had ileocolic disease and in one only the large bowel was affected. All five patients at some time underwent intestinal resection for Crohn's disease: three had a right hemicolectomy and two had a subtotal colectomy with ileosigmoid anastomosis. Of the hemicolectomies, one (patient No. 5; *Table 1*) was performed at the same time as the sphincter repair together with a rectopexy. The indication for rectopexy in this patient was a full thickness rectal prolapse on straining; the mesorectum was sutured to the sacral promontory but no mesh was inserted. Sphinter repair was performed before resection in two of the other patients and after resection in a further two.

All six patients were diagnosed clinically as having perianal Crohn's disease. One patient (No 6) had active disease with oedematous skin tags, abscess formation and a rectovaginal fistula and the diagnosis was confirmed histologically. In two patients (Nos. 3 and 4) there was quiescent disease with histological confirmation and in the remaining three patients the anal disease was quiescent and histological confirmation of anal disease was not obtained, although they were all known to have intestinal Crohn's disease.

Details of preoperative anorectal physiology were available in three of the six patients and confirmed an abnormal external sphincter with voluntary squeeze pressures of 35 cmH_2O or less. No postoperative studies of anorectal physiology have been performed.

A standard overlap type of repair was used in each case[7]. Prolene® (Ethicon Ltd., Edinburgh, UK) was used for the repair in one patient, nylon in another and stainless steel wire in the other four (*Table* 1). In one patient (No. 6) repair included closure of a rectovaginal fistula. In all but one of the six patients a proximal stoma was either present before operation or constructed as part of the operation (one terminal ileostomy, one loop ileostomy, one end colostomy and two loop colostomies).

Results

In one patient the deep part of the sphincter repair broke down and had to be repaired 16 days after operation. All five patients who had a stoma subsequently had it closed between 2 and 20 months postoperatively.

Of the six patients, one remained incontinent after operation and required a permanent colostomy. The remaining five patients are fully continent of flatus, liquid stool and solid stool (follow-up varies from 18 months to 16 years, mean 7·8 years).

The patient who remains incontinent has had no recurrence of intestinal or perianal disease. Of the other five patients, two (Nos. 1 and 4) still have signs of perianal Crohn's disease and four have had recurrence of intestinal disease.

Discussion

Perianal disease is a common feature of Crohn's disease[8,9] and a frequent indication for surgery[10]. However, it is hard to define anal involvement in Crohn's disease. Multiple fistulae associated with purulent discharge and abscesses clearly constitute active disease, and one of the patients in this survey who achieved a Grade 1 result was in this situation. However, small asymptomatic skin tags obviously do not represent active disease; patients with this clinical picture are expected to fare better after any sort of anorectal surgery. Indeed, if skin tags are included then anal lesions may be found in as many as 80 per cent of patients[11], but symptomatic anal disease (excluding skin tags) has been described in only a third (49 of 151 successive patients[12]) treated for Crohn's disease. In addition, fistula *in ano* may be incidental to intestinal Crohn's disease. Attitudes to sphincter surgery in anorectal Crohn's disease have been mixed[13,14] but, at the very least, the results

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Table 1 *Summary of results of sphincter repair in Crohn's disease*

	Patient					
	1	2	3	4	5	6
Age at operation (years)	34	12	29	48	24	34
Sex	F	F	F	M	F	F
Intestinal disease	IC	IC	IC	PA	IC	C
Duration of disease before operation (years)	7	7	0·5	?	8	7
Intestinal operation	RHC	STC	RHC	—	RHC	STC
Year of sphincter repair	1971	1972	1972	1975	1986	1986
Stoma	+	+	+	+	−	+
Material used	S	S	S	S	P	N
Closure of stoma (months after operation)	12	2	5	20	—	3
Cause of incontinence	Surgery	Surgery	Surgery	Surgery	Surgery	Obstetric
Result of operation (Grade)	1	1	1	1	3	1
Period of follow-up (years)	16	4	15	2·5	1·5	1·5

Patient No 2 died of a pulmonary embolus 2 years after colectomy; IC, ileocolic disease, C, colonic disease; PA, perianal disease only, RHC, right hemicolectomy; STC, subtotal colectomy; S, stainless steel; N, nylon; P, Prolene

presented here indicate that an incidental diagnosis of Crohn's disease should not preclude an attempt at anal sphincter repair.

A covering stoma is much less frequently used in conventional sphincter repair than previously but it seems a reasonable precaution when operating in Crohn's disease. The only patient who did not have a covering stoma had a poor result.

In conclusion, this highly selected group of patients with Crohn's disease who have undergone sphincter repair have not suffered complications of wound breakdown or fistula formation. Their functional results have been good. In the light of these results, which are similar to those achieved in patients without inflammatory bowel disease, it may be appropriate to consider sphincter repair in patients with mild or quiescent Crohn's disease when the alternative is proctocolectomy

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Totally stapled abdominal restorative proctocolectomy

A technique of totally stapled abdominal restorative proctocolectomy is reported in 20 consecutive patients using a 20 × 20 cm J pouch and a stapled ileoanal anastomosis. The stapled ileoanal anastomosis had to be abandoned in three patients because of attempted mucosectomy in one and megarectum in two. One patient receiving steroids had a covering ileostomy. The remaining 16 patients had a totally stapled procedure without a covering ileostomy. Three patients developed serious postoperative morbidity but they were the only patients receiving steroids at the time of the operation. Of the remaining 13 patients none developed serious complications, the median hospital stay was 14 days and the median operating time was 150 min. The operation may be a technical advance particularly in allowing pouch construction without ileostomy in fit patients who are not receiving steroids at the time of operation.

Keywords: J pouch, ileoanal anastomosis, restorative proctocolectomy, stapling device

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Restorative proctocolectomy with ileal reservoir and ileoanal anastomosis has now become an alternative to conventional proctocolectomy and end ileostomy for patients with ulcerative colitis, familial adenomatous polyposis and some forms of functional bowel disorder[1].

The aim of restorative proctocolectomy is to eradicate the entire disease-bearing colorectal mucosa while preserving anal sphincter function[2]. The high frequency of defaecation and episodic incontinence associated with straight ileoanal anastomosis has now largely been overcome by providing an ileal reservoir[3,4].

There is evidence of impaired sphincter function following anal mucosectomy during the operation of restorative proctocolectomy which is probably associated with prolonged anal retraction[5]. Evidence from some centres suggests that ileoanal anastomosis to the upper anal canal is associated with improved functional results when compared with conventional endoanal anastomosis to the dentate line[6]. This may be due partly to the avoidance of anal sphincter damage and preservation of the anal transition zone. A prospective randomized trial has indicated that the clinical result of a stapled J pouch was indistinguishable from the more time-consuming but theoretically larger W pouch[7].

If restorative proctocolectomy is to become widely adopted it is important that it should be a procedure that can be safely executed with minimal morbidity. The development of stapling instruments has allowed the operation to be accomplished by an experienced colorectal surgeon who has sufficient experience of stapling techniques[8,9]. Our own experience suggests that the totally stapled restorative proctocolectomy is associated with a lower morbidity than the conventional hand-sutured pouch construction and ileoanal anastomosis[10].

In 1988, 20 consecutive restorative proctocolectomies have been performed and in all of these operations a totally stapled procedure has been attempted. The operations were performed by a single surgeon (M.R.B.K.) with the help of one assistant and a scrub nurse. No special pelvic retractors were used.

Patients and methods

After a standard bowel preparation the patient is anaesthetized, catheterized and placed in the Lloyd-Davies position.

A long midline incision is used and the colectomy is performed in the usual manner with preservation of the ileocolic artery. The ileum is transected at the ileocaecal valve using the TA30®, GIA50® (US Surgical Corporation and Auto Suture UK, Ascot, UK) or proximate PCL50® (Ethicon Ltd., Edinburgh, UK) stapler. Unlike the hand-sutured ileoanal anastomosis, the duodenojejunal flexure and the origin of the superior mesenteric artery rarely need to be mobilized. The rectal dissection used by this surgeon involves radical mesorectal excision as in proctectomy for malignant disease. In this way there is no tissue in the posterior aspect of the pelvis to limit access to the upper anal canal. The posterior dissection proceeds immediately behind the superior haemorrhoidal artery, taking the mesorectum down to its limit at the anorectal junction. There should be no fear of damage to the pelvic nerve as these can be readily visualized crossing the pelvic brim. Damage to the autonomic supply to the prostate, seminal vesicles, bladder and vagina will be avoided provided the anterior plane lies well behind Denonvilliers' fascia. The rectum and the upper half of the anal canal must be completely mobilized. This is only possible by dividing Waldeyer's fascia between the rectum and the puborectalis sling. At this stage it is helpful to place a clamp across the upper anal canal at the proposed anastomosis site and to examine the anal canal digitally to ensure that at least 2 cm of anal canal is preserved above the dentate line.

A TA30 stapler is then applied across the upper anal canal at the desired distance from the dentate line (*Figure 1*) and the instrument is fired. The anal canal is transected above the staples and the rectum

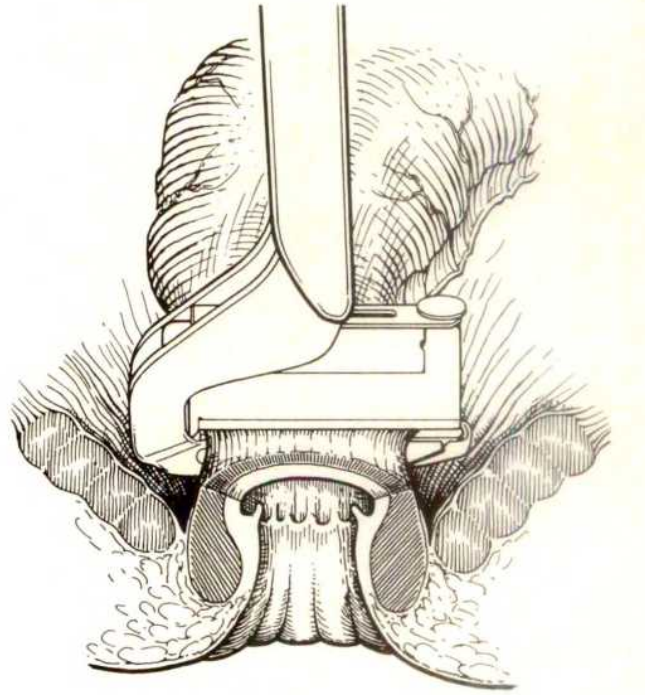

Figure 1 *Stapled transection of the upper anal canal using the TA30® stapler*

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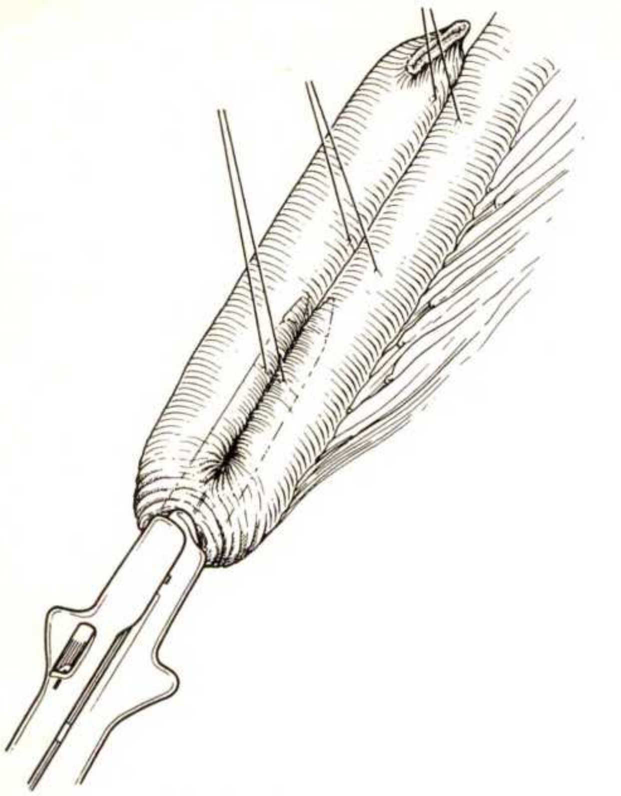

Figure 2 *Stapling of the two limbs of the J pouch using the long-bladed GIA90® stapler*

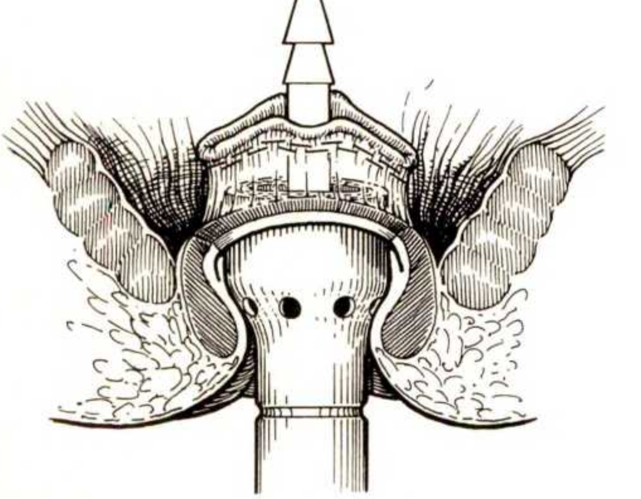

Figure 3 *Insertion of the central pin attached to the instrument head through the staple line of the previously transected anal canal*

removed. A double-limb J pouch 20 × 20 cm is measured and tested for length by placing a Duval clamp across the proposed apex of the pouch to ensure that it can be approximated to the stapled anal transection line. Using this technique the vessels in the small bowel mesentery have never needed to be divided. An enterotomy is made in the apex of the proposed pouch and the two limbs approximated by three stay sutures. The limbs of the pouch are stapled together using either two applications of the long GIA90® (US Surgical Corporation and Auto Suture UK; *Figure 2*) or three or four applications of the GIA50 or proximate PCL50 stapler. These instruments produce a double staple side-to-side anastomosis. To avoid multiple enterotomies the bowel is telescoped over the reloaded stapler, advancing beyond the previous staple line until both limbs have been anastomosed.

A purse-string 0 Prolene® (Ethicon Ltd., Edinburgh, UK) suture is placed around the enterotomy in the apex of the pouch. A 30 Fr Foley catheter is then inserted through the distal enterotomy and a non-crushing clamp is applied to the proximal small bowel. Saline 300–400 ml is introduced into the pouch to identify any leaks in the anterior and posterior staple line. This procedure also allows the evacuation of clot from the stapled pouch.

The ileoanal anastomosis is performed using the premium EEA® (US Surgical Corporation and Auto Suture UK) stapling instrument. The anvil of the circular stapler is removed and replaced by a pointed central pin. The central pin is retracted inside the instrument. The shoulders of the head are gently inserted into the short anal stump against the transected staple line. The central pin is then advanced while the abdominal surgeon checks by palpation and vision that the pin penetrates the centre of the anal staple line. The perineal operator then pushes the pin through the staple line aided by counter-pressure from above (*Figure 3*). After fully advancing the shaft, the pin is removed from the stapler head. The anvil of the stapler is inserted into the apex of the pouch through the previously inserted Prolene purse-string suture which is then tied around the anvil pin in the groove (*Figure 4*). The anvil pin can be snapped into the hollow end of the main shaft (*Figure 5*). The circular stapler is then closed until it is in the firing position on the gauge, the safety catch is released and the instrument is fired. Two concentric circles of staples are applied and a hole is cut within the inner staples. The tissue includes a short cylinder of anal canal and the apex of the pouch. The stapling instrument is unwound by two and a half counter-clockwise turns. The entire instrument is then rotated to ensure that the blade has completely divided both ends of the bowel and the instrument is then gently withdrawn through the anus by the abdominal surgeon who applies gentle traction on the pouch to disengage the stapling device.

The completeness of the two 'doughnut' rings is checked and the anastomosis is palpated through the anus to ensure that it is intact. The pelvis is then filled with saline, a non-crushing clamp is applied across the proximal small intestine and the absence of air leaks is verified by inflation of the pouch per anus using a 50 ml syringe. Provided there are two complete rings, no air leaks and the staple line appears to be intact on palpation, no covering ileostomy is raised.

Two closed suction drains are placed in the pelvis for 48–72 h. A 30 Fr latex catheter is inserted through the anal anastomosis into the pouch and sutured to the perianal skin. This catheter is used to irrigate the pouch with 50 ml saline 4-hourly for the first 3–4 days to remove haematomas. Irrigation stops when small bowel contents start issuing

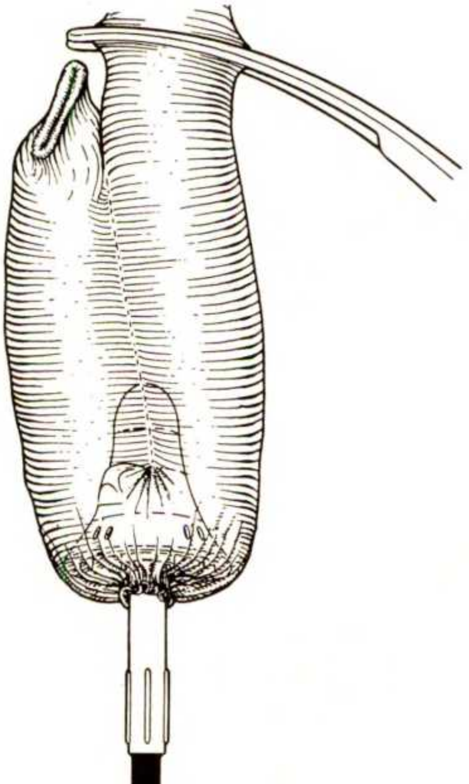

Figure 4 *Anvil secured in the J pouch by a purse-string suture at its base*

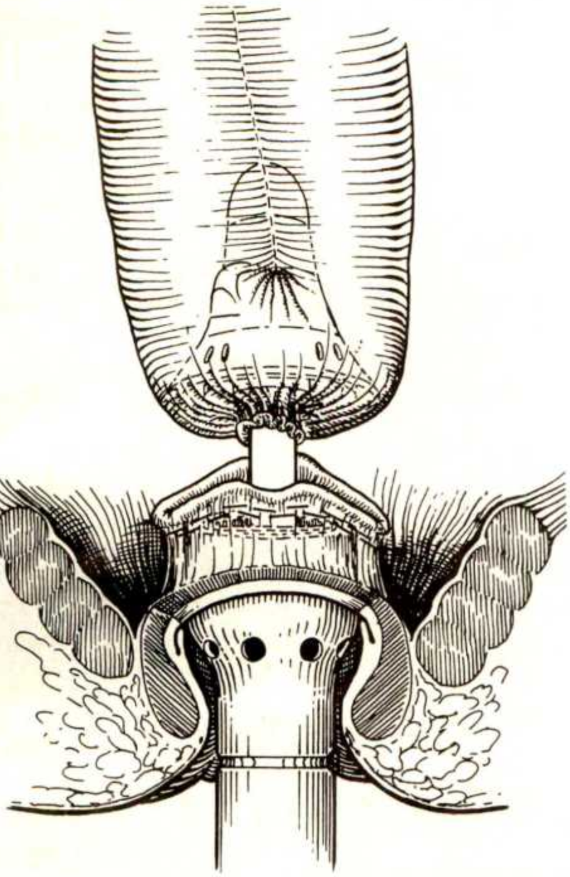

Figure 5 *Advancement of the anvil pin into the hollow end of the main instrument, thereby joining the J pouch to the anal canal*

from the catheter. The catheter then acts as a perineal ileostomy and is usually removed between 7 and 10 days after the operation. Most patients are able to be discharged from hospital 4–5 days later.

Results

Totally stapled restorative proctocolectomy has now been used in 20 consecutive patients since January 1988 (nine male patients, median age 30 years (range 16–60 years)). Fourteen patients had a diagnosis of ulcerative colitis, three had operations for familial adenomatous polyposis and three male patients had a megarectum due to aganglionosis. In 12 patients total colectomy, rectal excision and pouch construction were performed as a one-stage procedure, the remaining eight patients had had a previous colectomy, ileostomy and the rectal stump had been oversewn.

The median operating time was 155 min (range 120–220 min) and the median duration of hospital stay was 14 days (range 12–104 days). There were three operative technical failures. In the first patient an attempt was made to perform an abdominal mucosectomy; subsequent attempted transection of the anal canal was incomplete. In the other two patients, both of whom had a megarectum, the bowel was too dilated to allow the TA30 stapling instrument to be inserted around the mid-anal canal. All of these patients underwent a sutured ileoanal anastomosis which was protected by a loop ileostomy. Two of these patients have had uncomplicated ileostomy closures (2 and 3 months postoperatively) while the other patient awaits closure.

Of the remaining 17 patients only one had a covering ileostomy. This patient was receiving steroid therapy at the time of operation. Pouch construction was technically difficult and there was some persistent bleeding in the pelvis, hence a loop ileostomy was raised. The patient developed pelvic sepsis thought to be due to a pelvic haematoma. Despite this the loop ileostomy was subsequently closed without complication (hospital stay 22 days).

Sixteen patients had a totally stapled restorative proctocolectomy without a covering ileostomy. In three patients there was major morbidity. All three patients were receiving steroid therapy at the time of the operation. One patient developed Gram-negative shock due to peritonitis which was not evident clinically. There was no radiological evidence of leakage and air insufflation of the pouch at the time of laparotomy 7 days after the initial operation failed to detect leakage. Despite this, the proximal bowel was transected with construction of an end ileostomy and a mucous fistula (hospital stay 26 days). A second patient developed a pelvic haematoma and radiological evidence of leakage from the transected ileum. The ileoanal anastomosis was intact. The patient underwent construction of an end ileostomy and a mucous fistula 21 days after operation (hospital stay 37 days). One further patient receiving steroids at the time of operation, who has already been reported[11], developed an intussusception of the afferent limb resulting in proximal infarction of the pouch necessitating excision 5 days after the original operation (hospital stay 104 days).

Of the remaining 13 patients who had a totally stapled procedure without a covering ileostomy, only two developed minor complications: both were wound infections at the site of the previous ileostomy. The median hospital stay of these patients was 14 days (range 11–17 days). All of these patients at the time of discharge from hospital were fully continent during the day but two reported intermittent soiling at night necessitating the wearing of a pad. At the time of discharge the median frequency of defaecation was 6 (range 5–9) during the day and 1 (range 0–3) at night. Although the stool was generally fluid, all patients could defer defaecation for at least 30 min and all patients were able to discriminate between liquid stool and flatus.

Eight of these 13 patients who did not have a loop ileostomy have now been assessed at least 3 months after discharge from hospital. All remain continent by day but one patient still complains of soiling at night. The median frequency of defaecation is 5 times in the day (range 4–8) and once at night (range 0–3). All patients are able to defer defaecation for more than 1 h and seven of the eight now pass semisolid stools.

Discussion

The totally stapled pouch technique offers major advantages in terms of operating time and avoidance of a proximal ileostomy. In patients who have no major morbidity, the longest hospital stay was only 17 days and one patient was discharged 11 days after operation. A second admission was avoided and the known morbidity attending closure of a loop ileostomy was entirely eliminated[12]. The cost of the staples for this procedure is 435 pounds sterling, but the financial benefit of avoiding a second admission, usually for 8–10 days, is clearly outweighed by this reduction in total hospital stay when proximal ileostomy is avoided. Another potential benefit over other techniques described in the literature[8,9] is the use of the single distal enterotomy for pouch construction and the long-limbed GIA90 instrument. The distal enterotomy technique minimizes the risk of leakage when compared with multiple enterotomies for a stapled pouch construction[10,12].

In common with other authors[6,9] the mucosectomy has been abandoned as the ileoanal anastomosis is placed 1 cm above the dentate line. The worry in colitic patients of persistent colitis and of carcinoma in the small 1 cm cylinder of at-risk mucosa has not been borne out by clinical follow-up in patients where the anal transition zone has been deliberately preserved[13–15]. However, follow-up of these patients is short. In a recent cohort study of cancer risk in ulcerative colitis, 261 patients from Birmingham presented with ulcerative colitis between 1945 and 1975[13]. Of 2500 patient-at-risk years of developing malignancy, three rectal cancers presented. We have analysed these three patients and no tumour presented in the distal 3 cm of the rectal mucosa. Clearly the long-term cancer risk cannot be ignored[16]; however, this short cylinder of mucosa is easily accessible to the rigid sigmoidoscope and the examining index finger[6]. In one patient the retained mucosa has bled postoperatively, but this settled spontaneously. Biopsy did not reveal features of active colitis.

Using the described technique in which the mid-anal canal is stapled, the internal anal sphincter is partially excised. Nevertheless, no patient was incontinent, and anal pressures have been well preserved.

There were no episodes of small bowel obstruction. Previous studies identify adhesive obstruction as an important cause of morbidity but this may be partly related to a proximal ileostomy and its subsequent closure[12,15].

A number of important lessons emerge from this small consecutive series. The staple transection of the anus in patients with gross megarectum for aganglionosis is technically difficult as these patients are usually male. It is probably wiser under these circumstances to perform a conventional sutured ileoanal anastomosis which is covered by a loop ileostomy. The operation of one-stage totally stapled restorative proctocolectomy without a covering ileostomy is unwise in patients receiving steroid therapy. All three patients in this category developed major complications, one necessitating pouch excision and the other two requiring a difficult laparotomy and proximal intestinal diversion.

If, on the other hand, the patient is no longer taking steroids and there are no technical difficulties, the totally stapled restorative proctocolectomy is a major advance, both in the reduction of operating time and the avoidance of a proximal stoma. The anus must be transected well below the anorectal junction, preferably 2 cm from the dentate line, and no attempt should be made to perform a mucosectomy. If technical difficulties arise the ileoanal anastomosis may have to be hand-sutured using an intra-anal technique. Hence experience with these alternative techniques is essential before embarking on this modification of the operation.

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Obstructing carcinomas of the colon

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A series of 908 cases of colonic carcinoma has been analysed to elucidate reasons for the poor prognosis in obstructing colonic cancer. Complete obstruction was present in 148 cases (16·3 per cent), 280 cases (30·8 per cent) had partial obstruction and 480 (52·8 per cent) presented without obstruction. There were fewer Dukes' A tumours in those with complete obstruction ($P<0{\cdot}005$) *and greater numbers of advanced tumours* ($P<0{\cdot}0005$) *compared with those without obstruction. This is reflected in a lower curative resection rate of 50·7 per cent in those with obstruction compared with 70·6 per cent in those without obstruction* ($P<0{\cdot}001$)*. However, after curative resection there was no significant difference in the distribution of tumour stage. Patients with complete obstruction showed a higher incidence of recurrence* ($P<0{\cdot}01$) *after curative resection, consequent to an increased incidence of local recurrence* ($P<0{\cdot}02$)*. Five-year cancer-specific survival for the total series was decreased from 59·1 per cent in patients without obstruction to 31·8 per cent in those with complete obstruction* ($P<0{\cdot}001$)*. After curative resection there was also a significant reduction in survival* ($P<0{\cdot}001$)*. It is concluded that completely obstructing colonic cancers are more aggressive than other colonic cancers.*

Keywords: Colonic neoplasms, intestinal obstruction, neoplasm, carcinoma, recurrence, survival

The occurrence of large bowel obstruction secondary to colonic carcinoma has been reported in 7–29 per cent of colorectal cancer patients[1–6].

The survival rate of patients with obstructing colorectal cancers is significantly less than that of patients without obstruction[1–4,7–9]. In addition, there has been reported an increased risk of surgical mortality, a higher incidence of lymph node metastases, and a decreased curative resection rate[1–3]. Many factors have been suggested for the poor prognosis, including advanced age, poor general condition of the patient, advanced stage of the tumour, poorer differentiation, greater risk of vascular invasion, and delay in removal of the tumour which occurs when staged methods of resection are used[1–6,9–11].

The present paper has analysed clinicopathological and survival data in an attempt to explain the poorer prognosis

Patients and methods

Between 1950 and 1984, 1030 patients were operated on by one of the authors (E.S R H) for carcinoma of the colon. The series included patients with rectosigmoid cancers, but excluded rectal cancers. The colon has been divided into two segments, right and left, the junction being defined as the mid-transverse colon

Patients with perforation in addition to obstruction form a separate group of cases and are excluded from the present analysis, as are those with synchronous and metachronous cancers; this resulted in 908 patients being eligible for analysis.

Complete obstruction was diagnosed in patients presenting with absolute constipation, abdominal pain and distension, and dehydration, constituting an acute abdomen requiring urgent resuscitation and surgical intervention. This accounted for 148 (16·3 per cent) patients.

Partial obstruction was present in 280 (30·8 per cent) patients; it was considered to be present in patients with obstructive symptoms but still passing flatus per rectum who, in addition, had radiological features of incomplete obstruction, confirmed by colonic distension at laparotomy.

Four hundred and eighty (52 9 per cent) patients had no evidence of obstruction clinically, radiologically or at operation.

Clinical features, tumour pathology (including differentiation) and staging according to Dukes' classification[12] with, in addition, advanced disease according to Whittaker and Goligher[13], resectability, postoperative mortality, recurrence rates, and cancer-specific survival have been compared Advanced disease was subdivided into two categories, ‘D’$_1$ included tumours with local visceral invasion and ‘D’$_2$ included those tumours with distant dissemination.

All patients with colorectal cancer were prospectively registered and clinical, operative and pathological findings were recorded. The patients were followed by one of the authors (E.S R.H.) every 3 months for the first year, every 6 months for the subsequent 2 years, and then annually[14].

All the data were coded in a form suitable for computer analysis, using the Statistical Package for the Social Sciences[15]. χ^2 statistical analyses have been used throughout Cancer-specific survival curves have been plotted according to the conditional probability method of Kaplan and Meier[16]. Statistical differences between survival curves were evaluated by the generalized Wilcoxon test according to Gehan[17]. By this method, cases are classified as either fails (uncensored data) or non-fails (censored data). Fail signifies death due to colonic cancer. Non-fails were patients known to be alive or who had died from causes other than colonic cancer. Patients who died from complications occurring within 90 days of operation (63 postoperative deaths) were excluded from the cancer-specific survival analysis as were six patients lost to follow-up. The majority of the 839 patients eligible for analysis of cancer-specific survival have been followed up for periods of between 5 and 30 years

Results

There were no significant differences between the partial obstruction and non-obstruction groups in any of the findings, and therefore, to clarify the text, detailed results of the partial obstruction group are presented only in the *Tables* and *Figures*.

Incidence

Of patients without obstruction, 226 (47·1 per cent) were men and 254 (52·9 per cent) were women with a median age of 61·1 years (range 26–94 years). In those with complete obstruction 61 (41·2 per cent) were men and 87 (58·8 per cent) were women with a median age of 62·4 years (range 22–92 years).

Clinical features

The presenting symptom of abdominal pain in completely obstructing colonic tumours was present in 126 (85·1 per cent) patients compared with 284 (59·2 per cent) patients without obstruction ($P<0{\cdot}002$).

Abdominal distension was present in 103 (69·6 per cent) patients with complete obstruction compared with 32 (6·7 per cent) with no obstruction ($P<0{\cdot}0001$).

Symptom duration was less than 1 month in 45 (30·4 per cent)

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patients with complete obstruction compared with 109 (22·7 per cent) patients without obstruction.

Tumour distribution

Of the 908 patients in the total series, 288 were right-sided cancers and 620 were left-sided cancers. There were 37 (12·8 per cent) completely obstructing tumours of the right colon and 111 (17·9 per cent) of the left colon. The proportions of right-sided and left-sided tumours presenting with complete obstruction was not significantly different. The distribution is detailed in *Table 1*.

Management

The details of management are given in *Table 2*.

A potentially curative resection was defined as one where there was no evidence of macroscopic tumour remaining at the conclusion of the operation or of tumour at the lines of resection of the operative specimen, after histopathological examination.

The patients were treated by standard resections appropriate to the tumour site and the presence of obstruction. After the mid-1960s there was a preference for one rather than two or more stage procedures, and increased numbers of extended right hemicolectomies and subtotal colectomies were performed for distal obstruction. Twenty-four patients with stage 'D'$_1$ tumours underwent potentially curative resection.

Curative resections were performed on 75 (50·7 per cent) patients with complete obstruction. This incidence was lower than in patients without obstruction, 339 (70·6 per cent) patients ($P<0·001$).

Of the 75 patients with complete obstruction treated by curative resection 48 (64 per cent) patients had a primary resection and 27 (36 per cent) had a staged procedure. Only three patients without obstruction underwent a staged procedure.

Operative mortality

There were 13 postoperative deaths in patients with complete obstruction, a mortality rate of 8·8 per cent which was not significantly different from that in patients without obstruction (6·3 per cent: 30 deaths). After curative resection the postoperative mortality rate did not differ significantly between groups, being 6·7 per cent (five patients) and 4·4 per cent (15 patients), respectively.

The postoperative mortality rate in those with complete obstruction undergoing primary resection was 7 per cent (five of 70), which did not differ significantly from those undergoing staged procedures, 5 per cent (three of 57). After curative resection for one compared with two or three stage procedures for patients with complete obstruction, the postoperative mortality was 6 per cent (three of 48) and 7 per cent (two of 27), respectively, which did not differ significantly from that in patients without obstruction, 4·5 per cent (15 of 337) and zero (out of two), respectively.

The postoperative mortality rate after curative resection for right colonic tumours with complete or no obstruction was 3·7 per cent and 3·8 per cent, respectively. The corresponding mortality rates for left-sided tumours were 14·3 and 5·9 per cent. The differences were not significant.

The postoperative mortality rates after palliative resections in patients with complete obstruction and no obstruction were 6 and 14·5 per cent, respectively. The mortality rate after palliative bypass procedures in patients without obstruction was 7 per cent; no such procedures were performed in those with complete obstruction. Only one patient with complete obstruction underwent a diagnostic laparotomy alone and survived operation; the postoperative mortality rate was 5·9 per cent in the non-obstruction group.

The postoperative mortality for the periods 1950–65 and 1966–84 did not differ significantly between groups, both for the total series and after curative resection.

Pathology

Tumour staging. Tumour staging for the total series is detailed in *Table 3*. In the complete obstruction group there were only 11 (7·4 per cent) patients with Dukes' A tumours compared with 86 (17·9 per cent) patients in the group without obstruction ($P<0·005$). There was no significant difference in distribution of Dukes' B and C tumours. In the group without obstruction only 119 (24·8 per cent) patients had Dukes' 'D' tumours, which was significantly less than in the complete obstruction group where 58 (39·2 per cent) patients had Dukes' 'D' ($P<0·0005$).

Among those undergoing curative resection there were no significant differences in tumour stage distribution between patients with no obstruction or complete obstruction.

Tumour differentiation. Details of tumour differentiation were known in 316 patients without obstruction and 69 patients with complete obstruction. Tumour differentiation was divided into two groups, well differentiated tumours and other tumours

Table 1 *Tumour site distribution in 908 patients with colonic carcinoma*

	Right colon ($n=288$)	Left colon ($n=620$)
No obstruction	158 (54·9)	322 (51·9)
Partial obstruction	93 (32·3)	187 (30·2)
Complete obstruction	37 (12·8)	111 (17·9)

Values in parentheses are percentages

Table 2 *Surgical management of 908 patients with colonic carcinoma*

	Total	Curative resection	Palliative resection	Curative local excision	Palliative non-resection	Diagnostic laparotomy	Unknown
No obstruction	480	339 (70·6)	83 (17·3)	6 (1·3)	14 (2·9)	34 (7·1)	4 (0·8)
Partial obstruction	280	185 (66·1)	64 (22·9)	1 (0·4)	20 (7·1)	10 (3·6)	—
Complete obstruction	148	75 (50·7)	49 (33·1)	—	23 (15·5)	1 (0·7)	—

Values in parentheses are percentages

Table 3 *Tumour staging for the total series of 908 patients with colonic carcinoma*

	Total	Dukes' A*	Dukes' B*	Dukes' C*	Dukes' 'D'†	Unknown
No obstruction	480	86 (17·9)	156 (32·5)	87 (18·1)	119 (24·8)	32 (6·7)
Partial obstruction	280	42 (15·0)	95 (33·9)	44 (15·7)	94 (33·6)	5 (1·8)
Complete obstruction	148	11 (7·4)	44 (29·7)	20 (13·5)	58 (39·2)	15 (10·1)

Values in parentheses are percentages. * Dukes[12]; † Whittaker and Goligher[13]

Table 4 *Local and distant recurrence after curative resection*

	Total	No recurrence	Local only	Distant only	Local and distant
No obstruction	339	253 (74·6)	25 (7·4)	37 (10·9)	24 (7·1)
Partial obstruction	185	140 (75·7)	13 (7·0)	22 (11·9)	10 (5·4)
Complete obstruction	75	44 (58·7)	10 (13·3)	11 (14·7)	10 (13·3)

Values in parentheses are percentages

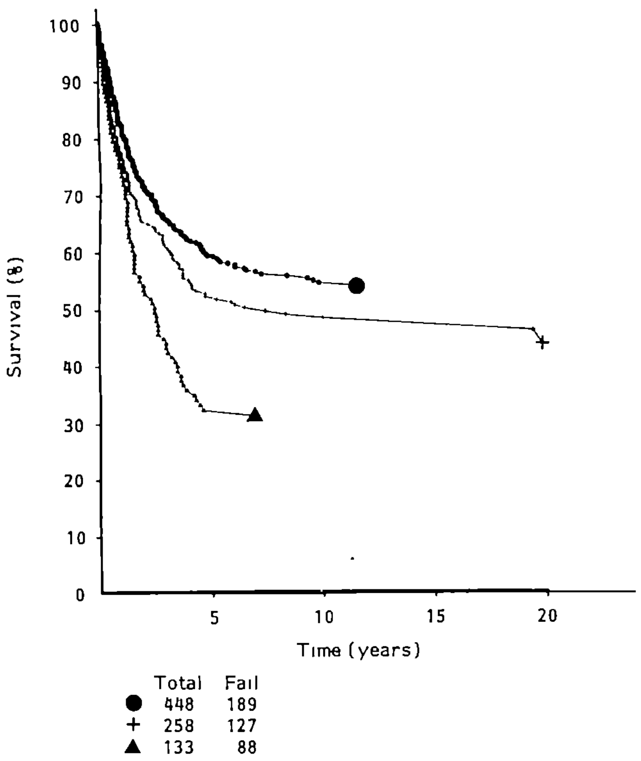

Figure 1 *Cancer-specific survival rates in relation to no obstruction* (●), *partial obstruction* (+) *or complete obstruction* (▲) *for the total series. Patients dying from complications within 90 days are excluded from the analysis Fail signifies death due to cancer of the colon; each mark on the survival curve represents an individual patient's death due to recurrent cancer of the colon. The heavier markings during the earlier postoperative years are consequent to an increased frequency of deaths during this period. Each survival curve attains a plateau after the last mark which represents the time of death of the patient who to date has survived the longest before dying from cancer of the colon The no obstruction and complete obstruction groups have been followed up for a comparable period to that of patients with partial obstruction. Survival is significantly worse comparing partial with no obstruction* ($P<0·04$) *and comparing complete with no obstruction* ($P<0·001$)

which included undifferentiated, poorly and moderately differentiated tumours. Forty-eight (15·2 per cent) tumours were well differentiated in those without obstruction. This incidence did not differ significantly from the 7·2 per cent (five patients) in those with complete obstruction.

Vascular invasion. There were no significant differences in the frequency of vascular invasion between patients with complete obstruction and no obstruction after curative or palliative resection.

Recurrence

Thirty-one (41·3 per cent) patients with complete obstruction developed recurrence (local and/or distant) after curative resection compared with 86 (25·4 per cent) patients in the non-obstructed group ($P<0·01$).

Details of local, distant, and local with distant recurrences are given in *Table 4*. Local recurrence was more frequent after complete obstruction compared with no obstruction ($P<0·02$), but distant recurrence did not differ significantly between groups.

Survival

Cancer-specific survival of patients with complete obstruction was significantly lower than for those without obstruction, both in terms of the total treated operatively and those managed by curative resection (*Figures 1* and *2*).

Cancer-specific survival rates after 5 years for patients with complete obstruction was significantly less than for patients without obstruction, being 31·8 and 59·1 per cent, respectively ($P<0·001$). After curative resection, 5-year cancer-specific survival rates were 54·1 and 78·9 per cent, respectively ($P<0·001$).

Cancer-specific survival after 5 years in patients with Dukes' A, B and C tumours who had curative resection are detailed in *Table 5*. For Dukes' B and C tumours there was a worse survival in patients with complete obstruction compared with no obstruction ($P<0·02$ and $P<0·05$, respectively).

Figure 3 compares cancer-specific survival in patients with complete obstruction undergoing primary and staged curative resections. Whilst the survival rate would appear to be improved for a primary resection (58·6 per cent 5-year cancer-specific survival) *versus* a staged resection (45·8 per cent 5-year cancer-specific survival), the difference did not reach significance ($P<0·13$). The same group of patients was further subdivided into right-sided and left-sided tumours (*Table 6*) Again, primary resection appears to show an increased survival compared with staged resections for both right and left colons but the difference was not significant. Nor was there a significant survival difference between right-sided and left-sided tumours.

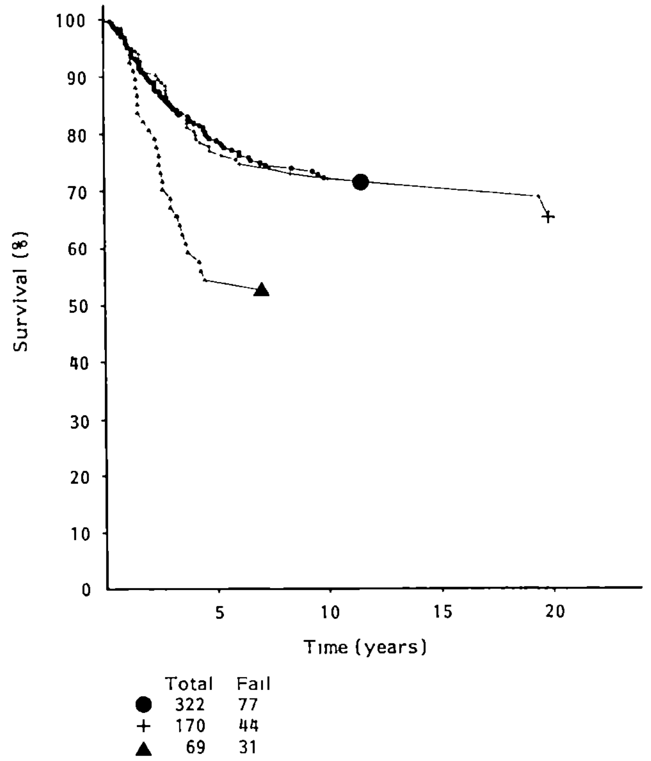

Figure 2 *The cancer-specific survival rate after curative resection is significantly poorer when complete obstruction* (▲) *is compared with no obstruction* (●) *or partial obstruction* (+) ($P<0·001$) *Each mark on the survival curves represents an individual patient's death due to recurrent cancer of the colon, fail signifies death due to cancer of the colon*

Table 5 *Five-year cancer-specific survival rates after curative resection for 520 patients with Dukes' A, B and C tumours*

	Dukes' A		Dukes' B		Dukes' C	
	No. of patients	5-year survival (%)	No. of patients	5-year survival (%)	No. of patients	5-year survival (%)
No obstruction	78	91·7	143	77·5	79	68·7
Partial obstruction	36	85·4	84	85·9	39	59·4
Complete obstruction	10	77·8	38	61·3	13	27·7

Table 6 *Five-year cancer-specific survival rates after primary and staged curative resection for complete obstruction*

	Right colon		Left colon		Total	
	No. of patients	5-year survival (%)	No. of patients	5-year survival (%)	No. of patients	5-year survival (%)
Primary resection	15	51·4	30	63·1	45	58·6
Staged resection	3	33·3	21	47·6	24	45·8

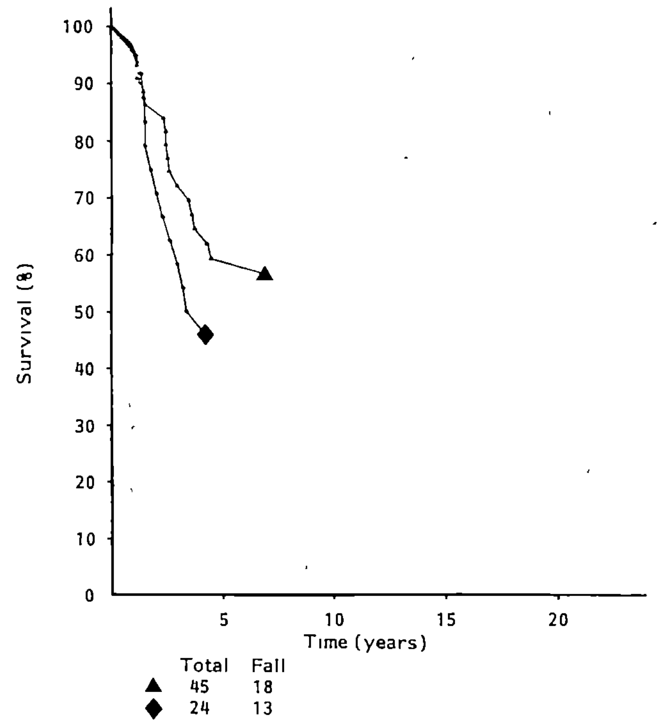

Figure 3 *The cancer-specific survival rate did not differ significantly between patients undergoing a primary (▲) or a staged (◆) curative resection for complete obstruction* (P<0·13). *Each mark on the survival curve represents an individual patient's death; fail signifies death due to cancer of the colon*

Comparison was made of cancer-specific survival for patients managed between 1950–65 and 1966–84. The 5-year survival rates were not significantly different comparing those having complete obstruction with those having no obstruction, both for the total series and after curative resection.

Discussion

The incidence of complete bowel obstruction due to colonic cancer (16·3 per cent) in this series closely resembles that reported by others[1–3,5,6,8]. The incidence of partial bowel obstruction (30·8 per cent) is considerably higher than that reported (10·2 per cent) by Ragland *et al.*[10]; however, the characteristics of those with partial obstruction have not previously been documented. The shorter symptom duration in patients with complete obstruction may point to a more rapid growth in obstructing cancers compared with non-obstructing cancers[18,19] Although there were greater numbers of left-sided obstructing tumours, as reported by others[5,20], the incidence of obstruction in the left colon compared with the right colon was not significantly different.

For the total series, in those with complete obstruction there were significantly fewer Dukes' A lesions and a greater number of Dukes' 'D' cancers compared with those without obstruction, which is in accordance with Umpleby and Williamson[3] and Dutton *et al.*[8], confirming that obstructing tumours were more locally advanced, with distant metastases being more common. This is reflected in the lower curative resection rate and poorer cancer-specific survival. The lower curative resection rate for completely obstructing tumours (50·7 per cent) compared with those without obstruction (70·6 per cent) is in agreement with several other series[1,3,21] but at variance with Dutton *et al.*[8] who reported a curative resection rate of 66·8 per cent in obstructed cases and a rate of 68·2 per cent for elective cases.

The postoperative mortality rate is based on the number of deaths due to complications occurring within 90 days of operation, and includes that of patients managed by staged resection. The mortality rates given are consequently approximately 1–2 per cent greater than those based on deaths occurring within 1 month of operation. The postoperative mortality rate after curative resection did not differ significantly between groups and attained 6·7 per cent for patients with complete obstruction. Other reports have given a considerably higher postoperative mortality rate in patients with complete obstruction of between 15 and 38 per cent[2,3,8,22–26], although in a related series of left-sided large bowel emergencies a rate of 8·5 per cent has been reported[27]. Furthermore, contrary to Waldron *et al.*[23,28], the mean age of patients in the groups varied from 60 to 63 years, those undergoing emergency surgery for obstruction being of a similar age to those undergoing elective procedures. This is reflected in a similar postoperative mortality rate for elective and emergency procedures.

In addition, contrary to these reports, the postoperative mortality rate did not differ significantly between primary and staged procedures, and is in accordance with Ohman[1]. Further, no significant difference in postoperative mortality rate was found comparing right-sided tumours with left, nor was there a difference in the periods 1950–65 and 1966–84. Hence we refute the suggestion by Waldron *et al.*[23] and Irvin and Greaney[2] that the worse prognosis is due to an increased perioperative mortality.

Several authors[1,5,22] have shown that the postoperative mortality rate for patients with complete obstruction has differed markedly between different surgeons, and that mortality has been less in patients operated on by consultant surgeons than by surgeons in training.

In the present series of patients with complete bowel obstruction, survival prospects did not differ between 1950–65 and 1966–84, both for the total series and after curative resection.

The poorer survival for patients with complete obstruction was not consequent to a higher postoperative mortality but to a decreased cancer-specific survival.

The cancer-specific survival was significantly reduced in patients with complete obstruction, for the total group, for those managed by curative resection, and for those with Dukes' B or C tumours.

The overall reduction in survival was related to an increased frequency of disseminated cancers, and this is in agreement with Willett *et al.*[29]. However, after curative resection the poorer cancer-specific survival was not related to any significant difference in tumour stage distribution, tumour differentiation, or degree of vascular invasion. In those with complete obstruction there was a significant increase in local recurrence and, although for those undergoing curative resection the stage distribution of tumours was similar, within Dukes' B and C tumours there was a significantly worse survival rate for those with complete obstruction. These findings suggest that colonic cancer presenting with complete obstruction is more aggressive than other colon cancers. It is not known whether the obstruction process itself influences the relationship between the tumour and host resistance. We conclude that there is another as yet unmeasured factor operating in those with obstruction resulting in the poorer prognosis.

In the present series, survival appeared to be improved for a primary *versus* a staged curative resection in patients with completely obstructing cancers, although the difference did not reach statistical significance. This finding is in accordance with Fielding and Wells[30], and others[2,3,31]. However, Ohman[1] and Phillips *et al.*[5] have reported opposing results, and further studies are required

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Anal canal mucosa in restorative proctocolectomy for ulcerative colitis

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In an attempt to improve continence after restorative proctocolectomy, ileal reservoir–anal anastomosis at the level of the anorectal junction has been advocated. This procedure preserves the entire mucosa of the anal canal. The histological appearances of the anal mucosa have been examined in 16 consecutive patients undergoing restorative proctocolectomy for ulcerative colitis. In 14 patients there was chronic inflammation characteristic of ulcerative colitis. Four patients had moderate dysplasia and in one of these patients an unsuspected adenocarcinoma of the anal canal extending down to the level of the dentate line was present. We believe that the anal mucosa should always be removed down to the level of the dentate line in restorative proctocolectomy for ulcerative colitis.

Keywords: Anus, restorative proctocolectomy, ulcerative colitis

Restorative proctocolectomy with ileal reservoir is now an established form of surgical treatment for ulcerative colitis and familial adenomatous polyposis The procedure satisfies the principles of excisional surgery for these conditions as it removes all diseased mucosa[1,2]. There has been considerable debate about which design of ileal reservoir produces the best functional results[3–5]. However, most have agreed on the importance of removing the entire anorectal mucosa as far as the level of the dentate line[3,4,6] because the anal canal may be lined with columnar mucosa down to this level[7], with consequent risk of neoplastic change

In an attempt to improve continence after restorative proctocolectomy Johnston *et al.* have carried out stapled reservoir–anal anastomosis at the level of the pelvic floor, thereby leaving intact the mucosa of the upper part of the anal canal[8]. We have examined the anal mucosa in a group of patients undergoing restorative proctocolectomy for ulcerative colitis to see how frequently the inflammatory process involved this area and to assess the potential danger of not excising the anal mucosa in this procedure.

Patients and methods

Sixteen consecutive patients undergoing restorative proctocolectomy for ulcerative colitis were studied A two-loop (J) reservoir was made in eight patients, a three-loop (S) reservoir in one, and the remaining seven patients had a four-loop (W) reservoir as previously described[4] The rectum was mobilized and divided at the level of the pelvic floor and the anal mucosa was removed peranally from the level of the dentate line up to the divided end of the anorectum. In some cases after mobilizing the rectum the muscle of the lower rectum was incised circumferentially and dissection was carried out in the submucosal plane down to the level of the anorectal junction The dissection was then completed by peranal excision of the anal mucosa from the level of the dentate line cranially to meet the abdominal dissection In each case the entire anal mucosa was removed down to the level of the dentate line.

Sections from the anal mucosa were taken from the dentate line to about the level of the anorectal junction and stained with haematoxylin and eosin The mucosa was examined with light microscopy for features of ulcerative colitis. Dysplastic changes were graded as mild, moderate or severe according to accepted criteria[9] Dysplasia was said to be present only when the cellular changes were considered to be beyond those that might accompany mucosal inflammation

Results

The anal mucosa was columnar proximally and squamous in the transitional zone in 13 patients, and in three patients the mucosa was columnar-lined down to the dentate line. Sections from 14 of the 16 patients showed chronic inflammatory changes characteristic of ulcerative colitis (*Figure 1a*) and in ten patients there was active inflammation. Moderate dysplasia was observed in four patients (*Figure 1b*). In one of these four patients there was invasive poorly differentiated adenocarcinoma of the anal canal, which extended down to the edge of the divided anal mucosa at the level of the dentate line (*Figure 2*). The rectum showed the severe inflammatory changes of chronic ulcerative colitis with mild dysplasia but the carcinoma was confined to the anal canal. Abdominoperineal excision of the pouch and anus with permanent ileostomy was carried out 2 weeks after the initial procedure.

Discussion

The presence of inflammation and dysplasia in the anal mucosa in a significant proportion of patients with ulcerative colitis in this study suggests that there may be a considerable risk in not removing the anal mucosa in restorative proctocolectomy. The rationale for leaving intact the mucosa of the upper anal canal in restorative proctocolectomy has been to improve the functional results of this procedure[8]. Some studies have reported a high incidence of minor degrees of incontinence after restorative proctocolectomy with ileoanal anastomosis at the dentate line[3,5,10] and Johnston *et al.* have suggested that continence is improved with stapled reservoir–anal anastomosis at the level of the anorectal junction compared with endoanal sutured anastomosis 1 cm above the dentate line[8].

Two possible mechanisms whereby this stapling technique might improve continence have been postulated[8]. First, the technique eliminates retraction of the anus during stripping of the anal mucosa and during ileoanal anastomosis. There is evidence that patients with minor incontinence after restorative proctocolectomy have lower resting anal pressures than patients with normal continence[8,11], indicating that internal anal sphincter damage may be the cause of the impaired continence. Nevertheless, some studies have found normal continence in over 90 per cent of patients after restorative proctocolectomy with excision of the anal mucosa[3,4] and, even allowing for differences

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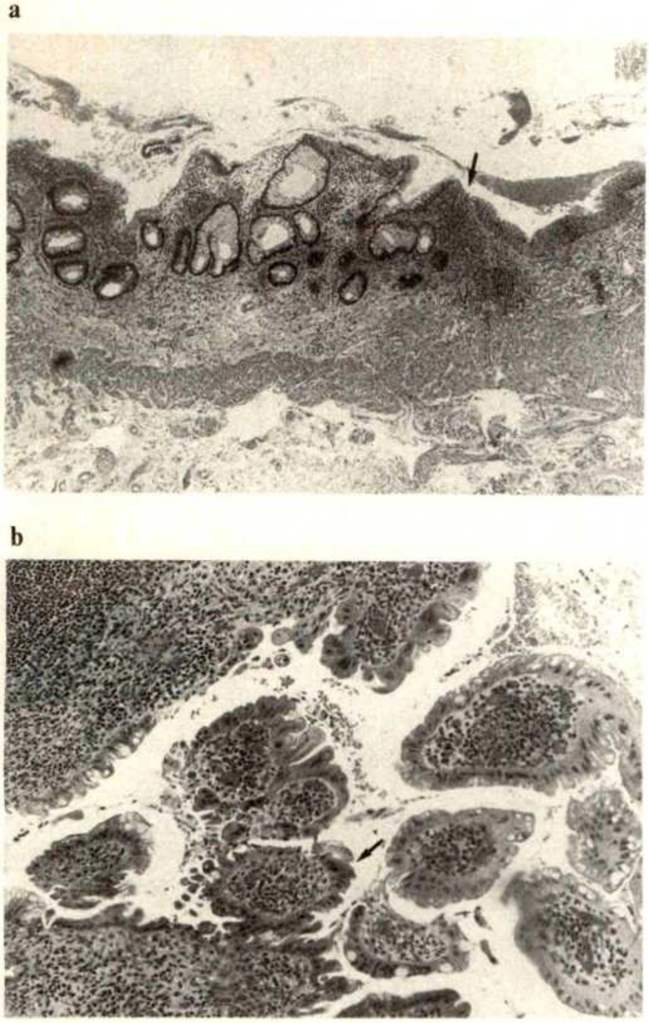

Figure 1 **a** *Anal canal mucosa showing the squamocolumnar junction (arrow). There is inflammation with ulceration, and crypt deformity and dropout*. **b** *Anal mucosa showing chronic inflammation, with mucosal dysplasia (arrow)*

in criteria for defining minor incontinence, it seems likely that normal continence can be achieved in the majority of patients by reducing the length of time of anal retraction.

Second, the stapling technique preserves the anal mucosa[8]. It has been suggested that the anal transitional zone, which extends from the dentate line to the columnar ('rectal') epithelium[7], as well as the columnar epithelium in the upper anal canal itself, may be important in maintaining continence after restorative proctocolectomy[8,12]. However the role of the anal mucosa in the normal continence mechanism remains uncertain[13]. 'Sampling' of the rectal contents by the anal mucosa is thought by some to be important[14] and apparent sampling responses have recently been found in ambulatory recordings of anorectal pressures[15]. However, anaesthetizing the anal mucosa does not impair continence in normal subjects[16]. Bartolo *et al.*[17] and Keighley *et al.*[18] showed objective evidence of reduced anal sensation after restorative proctocolectomy with excision of the anal mucosa including the transitional zone, as did Holdsworth and Johnston with excision of the mucosa to 1 cm above the dentate line[12]. However Keighley *et al.*[18] found in a small number of patients that this was not accompanied by impairment of continence or loss of the ability to discriminate flatus from stool. Furthermore, the high incidence of normal continence in some studies after excision of the anal mucosa[3,4,19] suggests that the anal mucosa was not essential for the preservation of continence in the majority of those patients.

The long-term risk of developing carcinoma in the rectum after ileorectal anastomosis for ulcerative colitis is only about 5 per cent with careful follow-up[20–22]. We have had no other case of anal adenocarcinoma occurring with ulcerative colitis. However, the small risk of developing anorectal carcinoma appears to be eliminated after total excision of the colonic and anorectal mucosa, which we believe should remain the fundamental aim of this procedure. Excluded islets of mucosal cells may be left behind after restorative proctocolectomy[23], but these cells have been shown not to be clinically relevant[24]. Early detection of anal carcinoma occurring adjacent to an ileoanal anastomosis might be difficult in some cases as induration or a slight irregularity might be attributed to the local effects of surgery.

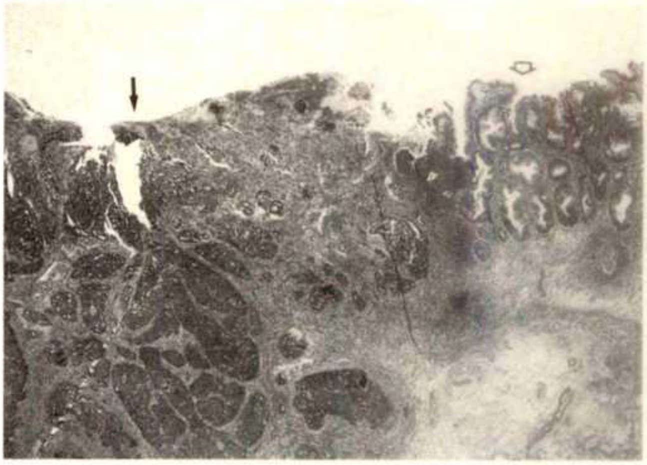

Figure 2 *Anal mucosa with columnar lining (proximal: open arrow), and invasive adenocarcinoma extending deeply into the submucosa (arrow). The anal canal was columnar-lined down to the distal surgical margin of the mucosa at the level of the dentate line*

It is possible that the histological changes observed in the mucosa in this study may have been modified by stripping of the mucosa. We have no preoperative anal biopsies to compare with the excised mucosa. Nevertheless, the major histological features were of chronic inflammatory changes with ulceration (*Figure 1*).

We were concerned that the anal carcinoma reported in this study was not recognized preoperatively. Examination of the histological sections shows a flat lesion with adjacent benign ulceration (*Figure 2*). Malignant change within this inflamed, ulcerated area was not even recognized by close inspection during endoanal mucosal excision.

Although the most distal part of the anal mucosa is usually not columnar epithelium, in a small proportion of patients in this study columnar epithelium was found down to the dentate line, as has previously been well described[7]. As it is not known whether this mucosa is squamous or columnar without histological examination, it is necessary to excise the entire transitional zone in all patients in order to remove the columnar epithelium in every case. Deasy *et al.*[25] found that the anal transitional zone was 'mildly inflamed' in 39 per cent of 31 patients undergoing total proctocolectomy for ulcerative colitis. However, 87 per cent of our patients had inflammation in the anal mucosa and in four of 16 dysplasia was present. For this reason, and because the transitional zone does not appear to be essential for normal continence, we would advocate complete excision of the anal mucosa in restorative proctocolectomy, with ileoanal anastomosis at the level of the dentate line.

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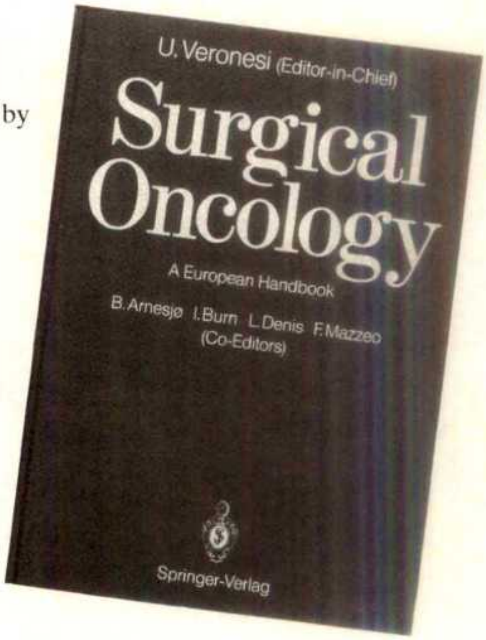
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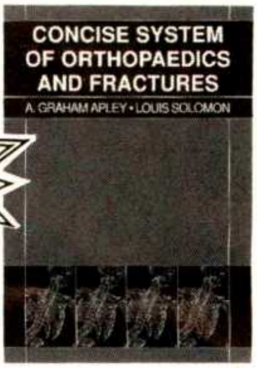
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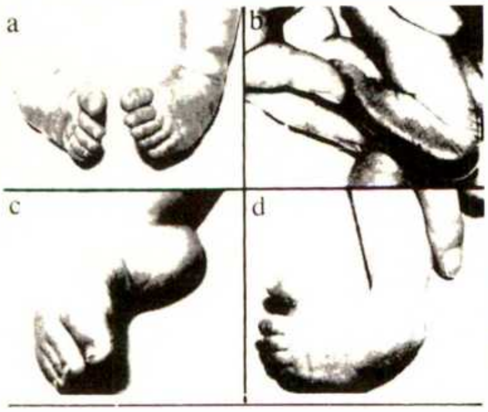

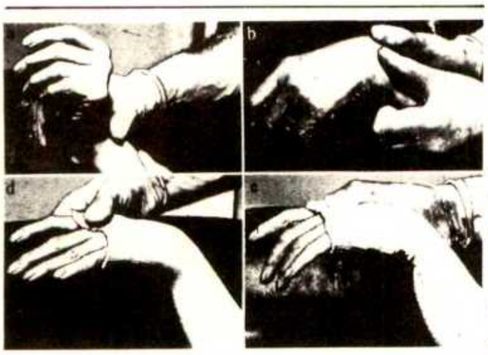

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Comparison of digital and manometric assessment of anal sphincter function

Anal sphincter function was assessed by digital examination and anal canal manometry in 66 patients and controls. Digital scores were allotted by using visual analogue scales for basal and squeeze sphincter function and were compared with the corresponding pressures. There were good correlations between digital basal score and maximum basal pressure (Spearman rank correlation coefficient $r_S = 0\cdot56$, $P < 0\cdot001$)*, and digital squeeze score and maximum squeeze pressure* ($r_S = 0\cdot72$, $P < 0\cdot001$)*. There were wide ranges of sphincter function on digital and manometric assessment with considerable overlap between patient groups. Digital scores detected differences in sphincter function between patient groups as accurately as manometry. The sensitivities and specificities of digital scores and anal canal manometry in segregating continent and incontinent patients were similar. It was concluded that digital estimation was equally as good an assessment of anal sphincter function as anal canal manometry.*

Keywords: Digital assessment, manometric assessment, anal sphincter function

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The primary function of the anal sphincters is to retain faecal matter within the rectum until a propitious time arrives for its controlled expulsion. Sphincter strength has been assessed by manometry using a variety of techniques[1]. The internal anal sphincter contributes 85 per cent of resting anal tone, and the external anal sphincter provides the squeeze increment[2]. Resting and squeeze anal canal pressures are reduced in faecal incontinence[3,4]. Other more sophisticated investigations such as fibre density measurement, pudenal nerve terminal motor latency[5] and motor unit potential duration[6] have demonstrated denervation of the external anal sphincter and puborectalis in idiopathic faecal incontinence.

Anal canal manometry, when available, often influences clinical decisions in anorectal surgery. Patients with low anal canal pressures will be offered abdominoperineal excision of the rectum for cancer, rather than a low anterior resection. Similarly, patients with low pressures are more likely to be incontinent after an ileoanal pouch procedure and might therefore be offered an end ileostomy.

However, the majority of general surgeons do not have access to anal canal manometry and their decision about which surgical procedure is appropriate in a case where continence is potentially threatened is based on assessment of anal sphincter function solely by digital examination.

The aim of this study was to compare digital estimation of anal sphincter function with a standard manometric measurement of sphincter tone, and to compare the ability of the two assessments of sphincter function to discriminate between the sphincter strength in groups of patients with faecal incontinence, severe constipation and normal control.

Patients and methods

Twenty-two asymptomatic subjects (20 women, two men, median age 43 years, range 38–47 years) undergoing minor surgical procedures unconnected with the anorectum, 22 severely constipated patients (20 women, two men, median age 35 years, range 19–47 years) and 22 faecally incontinent patients (21 women, one man; median age 66 years, range 50–85 years) were included in the study. The groups were matched for sex but the incontinent patients were significantly older than the other groups ($P < 0\cdot01$, Mann–Whitney *U* test)

With the patients lying in the left lateral position a digital rectal examination was performed and careful note was made of anal tone at rest and on a maximal voluntary contraction of the anal sphincter Marks were made on two separate non-continuous visual analogue scales (*Figure 1*), one for basal sphincter tone and one for squeeze tone The scales extended from zero at one end, representing no tone, to ten at the other end, representing the maximum tone conceivable Basal and squeeze scores were then allotted according to the position of the marks on the two scales. Analogue scales are the best available method of assessing subjective data, e.g degree of pain[7,8], and were felt to be the most appropriate method for digital assessment of anal sphincter function Once the marks for basal and squeeze scores had been placed on the scales the anal canal pressures were measured manometrically A water-filled system was used which consisted of a microballoon 4 mm in diameter connected to a Bell and Howell pressure transducer (Type 4-422-0001, Bell and Howell Ltd , UK), Lectromed amplifier (MX4P-145) and Lectromed chart recorder (Multi Trace 4; Lectromed Ltd , Jersey, UK) After calibration and determination of zero against the anal verge, the microballoon was inserted into the rectum. The pressures were recorded at rest and on a maximal voluntary squeeze contraction of the sphincter at 1-cm stations from 5 to 0 cm from the anal verge. The maximum basal pressure and maximum squeeze pressure were recorded[9]

The normal range, defined as including 95 per cent of the values obtained in the normal subjects, was determined for maximum basal

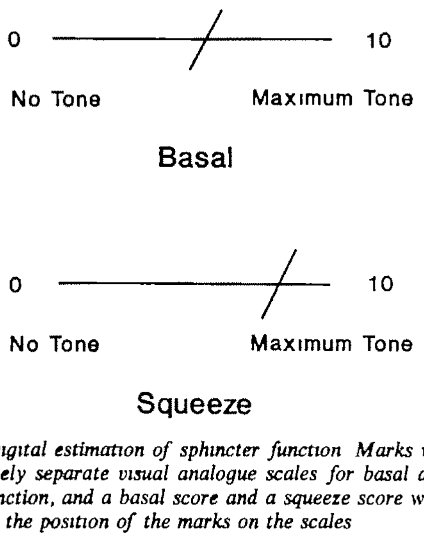

Figure 1 *Digital estimation of sphincter function Marks were placed on two entirely separate visual analogue scales for basal and squeeze sphincter function, and a basal score and a squeeze score were allotted according to the position of the marks on the scales*

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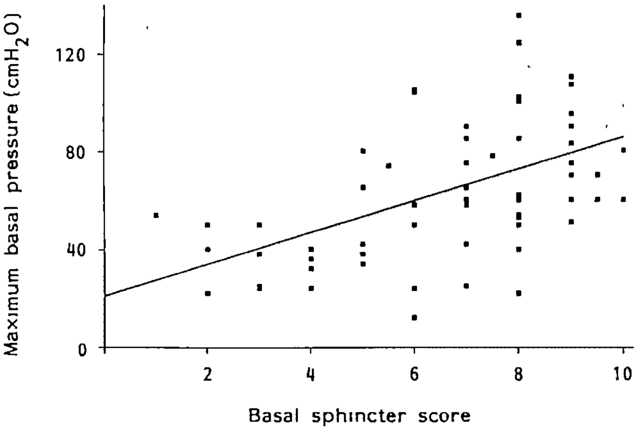

Figure 2 *Correlation of maximum basal pressure and digital basal sphincter score data from all patient groups:* $r_S=0{\cdot}56$, $P<0{\cdot}001$

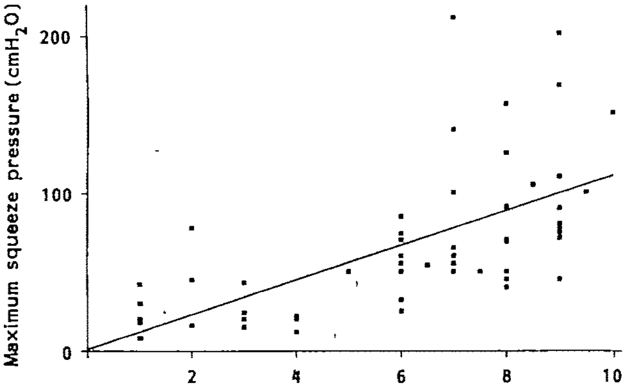

Figure 3 *Correlation of maximum squeeze pressure and digital squeeze sphincter score data from all patient groups*: $r_S=0{\cdot}72$, $P<0{\cdot}001$

pressure, maximum squeeze pressure, basal score and squeeze score. The lower limit of normal sphincter function was used to calculate the specificities and sensitivities of basal and squeeze manometric and digital sphincter functions, in discriminating between the continent and incontinent patients.

In a separate study the interobserver variability of digital and manometric assessment of anal sphincter function was compared in 14 patients. One investigator and one of three other surgeons experienced in anorectal physiology performed both digital and manometric assessment of sphincter function as described above.

All of the investigations were performed by the same surgeon (R.I.H.), with the exception of one arm of the interobserver variation study.

Spearman ranked correlation was used to compare manometric pressures and digital scores, and also for analysis of interobserver variation. The Mann–Whitney *U* test was used to compare patient groups after the Kruskal–Wallis test had demonstrated a difference.

Results

There was a significant correlation between maximum basal pressure and basal score ($r_S=0{\cdot}56$, $P<0{\cdot}001$; *Figure 2*) and a significant correlation between maximum squeeze pressure and squeeze score ($r_S=0{\cdot}72$, $P<0{\cdot}001$; *Figure 3*) when data from all patient groups were considered together.

There was a large overlap of basal anal sphincter function between all three patient groups for both maximum basal pressure and digital basal score (*Figure 4*). There was no significant difference between the control and constipated groups on manometry and digital score. The incontinent patients had a significantly lower basal sphincter function than the controls on both manometry ($P=0{\cdot}001$) and digital assessment ($P<0{\cdot}001$). The incontinent patients also had a significantly poorer basal sphincter function than the constipated patients on manometry ($P=0{\cdot}005$) and digital assessment ($P=0{\cdot}005$).

The findings for squeeze sphincter function were similar (*Figure 5*). There was a large degree of overlap of both maximum squeeze pressure and squeeze scores in all the patient groups. The incontinent patients had a significantly poorer squeeze function than both the control subjects ($P<0{\cdot}001$) and constipated patients ($P<0{\cdot}001$) on both digital and manometric assessment. Digital assessment detected a difference in squeeze function between the constipated and control patients ($P=0{\cdot}01$) which was not significant on manometry.

The sensitivities and specificities of manometric and digital assessment of basal and squeeze anal sphincter function in distinguishing the incontinent patients from the continent patients are shown in (*Table 1*). The sensitivities and specificities of maximum basal pressure and basal score were similar. The specificity of maximum squeeze pressure and squeeze score was similar, but the squeeze score was 21 per cent more sensitive than maximum squeeze pressure.

In the interobserver variation study there was a good correlation for maximum basal pressure ($r_S=0{\cdot}77$, $P=0{\cdot}001$), but not for basal score ($r_S=0{\cdot}49$, $P=0{\cdot}07$). There was a good correlation for maximum squeeze pressure ($r_S=0{\cdot}66$, $P=0{\cdot}01$) and also for the squeeze score ($r_S=0{\cdot}72$, $P=0{\cdot}004$).

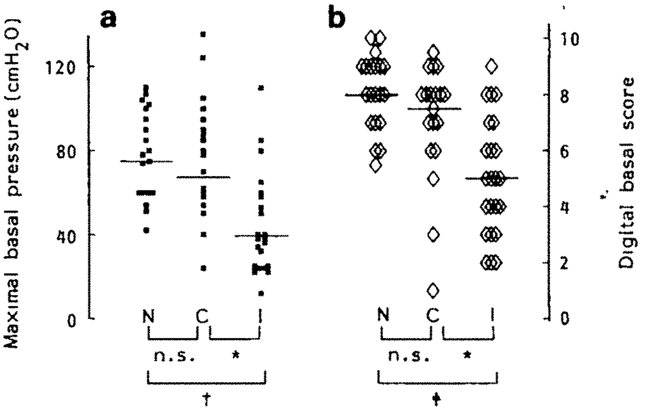

Figure 4 *Comparison of* **a** *maximum basal pressure and* **b** *digital basal score for normal control subjects (N), severely constipated patients (C) and incontinent patients (I). The solid horizontal lines indicate the median for each patient group,* *$P=0{\cdot}005$, †$P=0{\cdot}001$, ‡$P<0{\cdot}001$, *n.s., not significant (Mann–Whitney* U *test)*

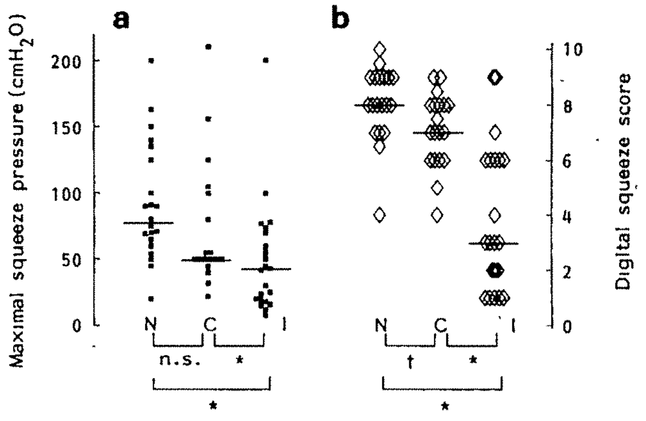

Figure 5 *Comparison of* **a** *maximum squeeze pressure and* **b** *digital squeeze score for normal control subjects (N), severely constipated patients (C) and incontinent patients (I). The solid horizontal lines indicate the median for each patient group;* *$P<0{\cdot}001$, †$P=0{\cdot}01$, *n.s., not significant (Mann–Whitney* U *test)*

Table 1 *Specificity and sensitivity of digital and manometric assessment of basal and squeeze anal sphincter function in distinguishing incontinent and continent patients with anorectal symptoms*

	Maximum basal pressure (%)	Digital basal score (%)	Maximum squeeze pressure (%)	Digital squeeze score (%)
Specificity	81	76	75	71
Sensitivity	59	59	56	77

Continence was used as the basis for calculation of specificities and sensitivities

Discussion

We have shown a significant correlation between digital and manometric assessment of basal and squeeze anal sphincter function. Felt-Bersma *et al.*[10] have also compared digital and manometric assessment of anal sphincter function. These authors characterized basal and squeeze sphincter strength into four groups (weak, moderate, normal and high) and their correlation coefficients were almost identical to ours. They did not compare the ability of manometry and digital estimation to discriminate between the sphincter function of different patient groups Two publications have commented that digital estimation does not correlate with anal canal manometry, but neither gave details of methods of comparison or the data on which the conclusions were based[3,11]

There was a wide range of anal canal pressures and digital scores in each of the three patient groups, with considerable overlap similar for manometric and digital estimation. Despite the overlap, digital estimation was able to discriminate sphincter function between the patient groups as effectively as anal canal manometry.

The sensitivities and specificities of digital estimation of anal sphincter function in discriminating symptomatic patients with and without incontinence were acceptable and similar to manometry. The squeeze score, however, had a higher sensitivity of 77 per cent; maximum squeeze pressure had a lower sensitivity of 56 per cent.

The remarkable similarity in the ability of anal canal manometry and digital estimation to discriminate between continent and incontinent sphincters is a tribute to the dense sensory innervation of the index finger. In addition anal canal manometry assesses only limited aspects of internal and external anal sphincter function, which themselves form only a part of the anal continence mechanism. The degree of sphincter recruitment in response to stress as well as absolute strength is of importance in the maintenance of continence[12]. The puborectalis muscle[13], rectal sensation, stool consistency[14] and sampling of rectal contents by the anal transition zone[15] are other important factors. A role has also been suggested for the anal cushions[16]. Digital estimation may perhaps give a more global assessment of the continence mechanism than manometry, which can only measure, perhaps with greater accuracy, internal and external anal sphincter strength.

We are aware of the potential bias of the investigator knowing the patient's diagnosis before undertaking the digital and manometric assessment of anal sphincter function. Bias in allocating the digital scores would tend to lead to a greater segregation of the patient groups on digital assessment than on manometry. However, the overlap between the patient groups was very similar for digital scores and anal canal pressures, and we therefore do not believe that the results of this study can have been influenced significantly by this particular bias.

In conclusion we have demonstrated a good correlation between digital scores and anal canal pressures and have shown that digital assessment is as good as manometry in discriminating sphincter function between continent and incontinent patients. We believe that manometry retains a definite place in clinical assessment and research, especially in prospective studies where the same individual is unlikely to perform all investigations. Manometry when interpreted in conjunction with other anorectal physiological investigations, e.g. electromyography and integrated pressure–electromyographic proctography[17], provides valuable information.

Optimal assessment of anorectal function in complex cases should include these investigations. However, as a single investigation for clinical purposes, there is little to choose between digital and manometric assessment of anal sphincter function.

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Role of dietary restriction in Haemoccult® screening for colorectal cancer

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The aim of this study was to investigate the effect of dietary restrictions on the positivity rate and yield of neoplasia during a study based on Haemoccult® screening for colorectal neoplasia. Of 18 925 participants who completed Haemoccult tests on a normal diet, 647 (3·4 per cent) were positive. All repeated the test with dietary restrictions: 251 remained positive and underwent further investigations which revealed 35 carcinomas and 169 adenomas in 129 subjects. The remaining 396 were sent a further Haemoccult test at 3 months. Of these, 317 (80·1 per cent) completed the test: 31 (9·8 per cent) were positive. Further investigation of the 31 positive subjects revealed four carcinomas and 20 adenomas. Retesting with dietary restriction will reduce the false positive rate of Haemoccult when used for colonic cancer screening. However, if the retest is negative a further test should be performed. To minimize the adverse effect this may have on compliance, we have allowed an interval of 3 months to elapse before this retest is requested.

Keywords: Colorectal carcinoma, screening, faecal occult blood

Faecal occult blood tests are the most widely used screening tests for colorectal neoplasia and have been shown to detect asymptomatic carcinomas at a less advanced pathological stage than those occurring in a matched control population[1–3].

Although increased blood losses have been shown in association with colorectal carcinoma, there is wide variation and an overlap with blood loss occurring in normal individuals[4,5]. A compromise in the sensitivity of the test for blood has to be reached whereby the maximum number of carcinomas are detected without subjecting a large number of healthy individuals to a potentially hazardous investigation such as colonoscopy.

The Haemoccult® (Röhm Pharma, Darmstadt, FGR) test is the most widely used for screening purposes and is considered to have a sensitivity suitable for the above requirements. It comprises a guaiac gum impregnated paper; the haematin moiety of haemoglobin catalyses the oxidation of guaiac to yield a colour change on the application of hydrogen peroxide. However, foods containing naturally occurring peroxidase and ingested animal haemoglobin may also result in a positive reaction. To minimize the incidence of such false positive reactions, testing with strict dietary restrictions has been advocated, avoiding the foods listed in *Table 1*, both when rehydration of the test slide has been performed[6] and without rehydration[7], although Macrae *et al.*[6] recommended immediate investigation if rehydration was not used.

We feel that such an imposition is an inconvenience to the participants in a population screening study and have demonstrated a statistically significant decline of up to 30 per cent in compliance when this has been employed (W. M. Thomas and J. D. Hardcastle, unpublished results) For this reason, routine dietary restriction is not employed at the initial screen in the Nottingham colorectal cancer screening study. All patients with positive results are subsequently retested with dietary restrictions and only proceed to further investigation if they remain positive for faecal occult blood. However, because of the known pattern of intermittent bleeding from tumours[4], it is thought prudent to perform a further test in those who are negative following dietary restriction (i.e. those who have had one positive and one negative test). In order to avoid repeated testing in a short period of time, we elected to delay this test by 3 months, a period decided upon as being reasonable to the participants in the screening study.

Patients and methods

Following the successful completion of a pilot study[8], a controlled trial of faecal occult blood screening for colorectal carcinoma was started in Nottingham in 1984 This is now the largest randomized controlled trial worldwide[1].

Participants in the trial, aged 50–74 years, are identified from general practitioner registers After stratification by age and sex, they are randomized by household into a test group, who are sent faecal occult blood tests, and a control group who do not receive the tests. The development of colorectal neoplasia in both groups is monitored by scrutiny of the pathology records of the Nottingham hospitals, by the Trent Region Cancer Registry and by information supplied by general practitioners. Development of neoplasia in people leaving the area is monitored using the National Health Service Central Registry.

The test group were sent either 3-day or 6-day Haemoccult test packs, together with an explanatory letter from their family doctor inviting them to complete and return the test. These tests were performed without dietary restrictions. The completed Haemoccult slides were tested, without rehydration, and a blue discoloration at 30 s was considered a positive result. From May 1986, those individuals with a positive test were asked to repeat the test with standard dietary restrictions, including red meats and vegetables high in peroxidase (*Table 1*). If this test remained positive, the patient underwent a colonoscopy and, if necessary, a double-contrast barium enema. If the test was negative, the patient was not investigated but was asked to perform a further test with dietary restrictions after an interval of 3 months.

Cancers were staged according to Dukes' classification[9], to which was added a Dukes' 'D' for patients presenting with distant metastases or locally unresectable disease.

Results

During the test period, 18 925 people agreed to participate in the study (*Figure 1*). After the initial request to perform Haemoccult tests (i.e. without dietary restrictions), 647

Table 1 *Foods likely to produce a false-positive Haemoccult test*

Red meat	Broccoli
Dark fish	Cauliflower
Black pudding	Parsnip
	Swede/turnip
	Radish/horseradish
	Banana

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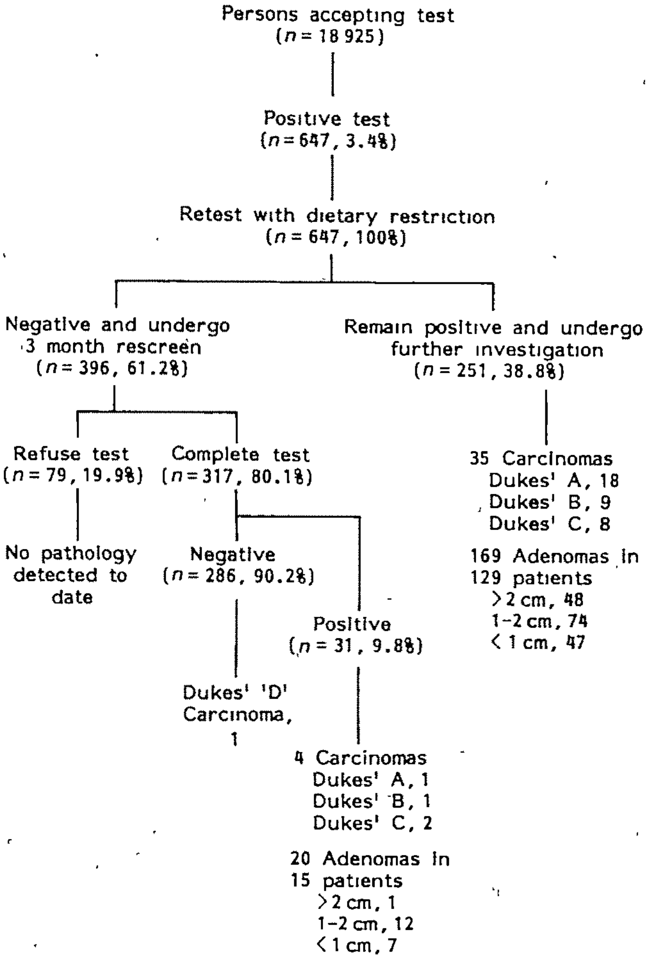
Persons accepting test (n = 18 925)
Positive test (n = 647, 3.4%)
Retest with dietary restriction (n = 647, 100%)
Negative and undergo 3 month rescreen (n = 396, 61.2%)
Remain positive and undergo further investigation (n = 251, 38.8%)
Refuse test (n = 79, 19.9%)
Complete test (n = 317, 80.1%)
35 Carcinomas
Dukes' A, 18
Dukes' B, 9
Dukes' C, 8
No pathology detected to date
Negative (n = 286, 90.2%)
169 Adenomas in 129 patients
>2 cm, 48
1-2 cm, 74
<1 cm, 47
Positive (n = 31, 9.8%)
Dukes' 'D' Carcinoma, 1
4 Carcinomas
Dukes' A, 1
Dukes' B, 1
Dukes' C, 2
20 Adenomas in 15 patients
>2 cm, 1
1-2 cm, 12
<1 cm, 7

Figure 1 *Outcome of screening by faecal occult blood test*

(3·4 per cent) were positive for faecal occult blood. They were asked to repeat the test with dietary restrictions (a compliance of 100 per cent was obtained): 251 people remained positive and were referred for further investigation. Thirty-five carcinomas (18 Dukes' A, nine Dukes' B and eight Dukes' C) and 169 adenomas in 129 patients were identified.

The 396 people who were negative for occult blood on dietary restriction testing were asked to participate in a further Haemoccult test at 3 months. Of these, 317 completed and returned the test, a compliance rate of 80·1 per cent; 286 (90·2 per cent) were found to be negative and 31 (9·8 per cent) positive. Investigation of the positive subjects revealed four carcinomas (one Dukes' A, one Dukes' B and two Dukes' C), and a total of 20 colonic polyps in 15 patients. These were all removed endoscopically; 17 were retrieved for histological examination, which demonstrated one villous adenoma, 11 tubulovillous adenomas and five tubular adenomas.

The median follow-up of these patients is 24 months, with a range of 18–33 months. To date, one patient in this group has presented with a symptomatic carcinoma 11 months after a negative test. He was found to have a carcinoma of the rectum with liver metastases.

None of the 79 patients who failed to complete and return the 3-month test has subsequently presented with large bowel neoplasia.

Discussion

Controversy persists regarding the ideal sensitivity of faecal occult blood tests used for screening purposes, and the role of dietary restrictions in those tests known to be affected by ingested animal haemoglobin or vegetable peroxidases.

The Haemoccult test is cheap, simple to perform and requires minimal laboratory expertise to interpret. In this study, 2·06 carcinomas and 7·61 patients with adenomas were detected per 1000 patients accepting the test[1]. The present rate of detection in the Nottingham trial is 2·30 carcinomas and 8·00 people with adenomas per 1000 accepting the test[1]. The randomized controlled trials have demonstrated that a significantly greater proportion of cancers detected by faecal occult blood tests are Dukes' A when compared with those occurring in the control populations[1–3]. Faecal occult blood tests are the most cost-effective method available for screening for colorectal neoplasia. The most expensive item in such a screening programme is the provision of endoscopic and radiological services to examine those individuals with positive tests. The adoption of a highly sensitive test for faecal occult blood, or a failure to allow for dietary factors, would result in the investigation by colonoscopy of many healthy individuals, producing a waste of available resources.

Retesting with dietary restriction has been advocated as a means of reducing the rate of dietary false-positive results and subsequent colonoscopy. Elliot *et al.*[10] used a further test after a 6-month interval in an attempt to minimize the number of false negative tests following a period of dietary restriction. No further cancers were detected in this series, although only half of those eligible had been retested at the time of the report.

In our study, 647 colonoscopic examinations would have been performed had retesting with dietary restriction not been employed. In fact 251 were performed following the initial retest, and a further 31 following the 3-month retest. Thus a saving of 365 (56·4 per cent) colonoscopies was achieved.

In addition to the financial savings, it is important to remember that unnecessary colonoscopy is an inconvenience to both patient and employer. Furthermore, there is a small but definite risk of a major complication, such as colonic perforation[11]. One carcinoma was probably missed at the time of the 3-month rescreen and this might have been detected if all those patients with positive tests at the initial screen had been investigated. However, had this been the policy, it would have been necessary to perform an additional 365 colonoscopies, greatly increasing workload and the risk of iatrogenic injury.

Although 100 per cent compliance was achieved for the initial request to repeat the test with dietary restrictions, it is of some concern that there was a deterioration in compliance at the 3-month rescreen, 79 (19·9 per cent) of those invited failing to complete this test. Of those who did complete the 3-month retest, four (1·3 per 100) were shown to have a carcinoma. This compares with an annual incidence of 0·1 per 100 persons in this age range, calculated from the age-specific incidence rates for England and Wales[12]. It would therefore appear that those who did not comply with the request to perform the 3-month rescreening test are at an increased risk of harbouring an asymptomatic carcinoma. However, with a median follow-up of 2 years, no such individuals have yet presented with symptomatic neoplasia.

As expected, the yield of neoplastic disease at the 3-month rescreening test is lower than that obtained in the select group in whom Haemoccult tests remained positive following a period of dietary restriction. Nevertheless, a further four carcinomas and 17 adenomatous polyps were detected, and the positive predictive value of the test for neoplasia is high (61·3 per cent) in this group.

There is no ideal faecal blood test for the detection of colonic neoplasia and a balance has to be achieved between the maximum detection of neoplasia and the minimum investigation of healthy individuals. At present we conclude that retesting with dietary restriction as described is justified, reducing the need for unnecessary investigations. However, there is a significant yield of neoplasia from the 3-month rescreening test and we advocate such testing for this group.

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Case report

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Pneumoparotitis

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Pneumatic inflation of the parotid gland can be an occupational hazard in glass blowers and those who play wind instruments[1–6]. It has also been reported in children as an attention-seeking device[2,3].

Case report

A 29-year-old man complained of a 'squelching' noise and feeling in the right side of his face and ear. The problem had been present for 2 years, was worse in the morning and had remained constant except for exacerbations associated with upper respiratory tract infections. On inspection there was no facial abnormality. Palpation of the right side of the face elicited a 'squeaking' noise on movement of the tissues overlying the right parotid gland. This was not immediately recognizable as the characteristic feel of surgical emphysema but when the right parotid was milked, air bubbles were noticed coming from the duct whose orifice was grossly dilated. No underlying social or occupational factors were elicited.

Plain radiographs and an ultrasound scan of the area were normal but a right parotid sialogram showed dilated ducts containing air. During investigation it was noted that the buccinator on the right had little activity and the cheek was allowed to balloon out on blowing. It was considered that the normal sphincter mechanism of the buccinator muscle was inefficient.

The patient was anxious to receive treatment; the operation described by Wilkie and Brody[7] for the treatment of drooling was advised. The duct was lengthened and posteriorly repositioned by using a buried mucosal flap based on a periductal pedicle. The new orifice of the parotid gland came to lie at the anterior pillar of the fauces to which it was sutured. The anterior defect was closed primarily.

The patient made a satisfactory postoperative recovery, with the complete disappearance of his previous symptoms. He was discharged from follow-up after 4 months.

Discussion

Expiratory intraoral pressure is normally 2–3 mmHg. Maximal pressures of 140–150 mmHg may be recorded in glass blowers and trumpet players[3,4]. The incidence is highest in those who blow with full cheeks as opposed to those who blow with the cheeks contracted[3].

Passage of air into the parotid gland is prevented by the contracted buccinator muscle which compresses the duct, and distension of the cheek which increases the angulation of the duct at the point where it turns medially at the anterior border of masseter. Furthermore, the diameter of the duct orifice is smaller than the diameter of the duct itself, and the duct is usually slit-shaped with mucous membrane folds which seal when the intraoral pressure is raised[3].

The condition may be complicated by infection[1] or by the accumulation of secretions in dilated portions of the gland or duct. Rarely there may be extension of the emphysema into the subcutaneous tissues of the neck so requiring the possibility of a pneumothorax or rupture of a laryngocele to be considered[5].

The treatment of pneumoparotitis in adults has so far been unsatisfactory. However, the problem in children appears to be self-limiting and no treatment is required. Methods of promoting the flow of saliva and air from the gland have been suggested such as the use of local anaesthetic to block the periarterial sympathetic nervous system at the level of the superficial temporal artery so relaxing the sphincter of Stenson and contracting the ducts. This has been used in conjunction with infiltration of antibiotics directly into the duct[6]. Surgical treatment has included unsuccessful efforts to close off the orifice of the duct with small clamps, excision of the duct and the majority of the glandular tissue or simple ligation of the duct[5]. Finally, patients have been advised to change employment[6]. However, the method of surgical treatment suggested which is both well tried and certainly, in this case, successful would remove the need for this drastic piece of advice.

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Acute primary hyperparathyroidism: experience of 59 cases

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Acute primary hyperparathyroidism is a rare disease with a high mortality rate in some series. Between 1960 and 1986, 1000 patients were treated for primary hyperparathyroidism, among them 59 patients with acute hyperparathyroidism. All these patients were successfully operated on; none of them died before surgery. This study reveals the importance of resuscitation and urgent surgery. It is necessary to rehydrate, to correct electrolyte disorders and to lower serum calcium levels, but it is not necessary to obtain normal serum calcium levels before surgery.

Keywords: Acute primary hyperparathyroidism

Between 1960 and December 1986, 1000 patients were treated for primary hyperparathyroidism in our department. Fifty-nine of these patients (5·9 per cent) had acute hyperparathyroidism and underwent surgery. One patient died

Analysis of these records enabled us to put forward our diagnostic and therapeutic experience, and to emphasize the importance of resuscitation and urgent surgery. In most cases, patients underwent surgery within 48 h of admission to our department.

Patients and methods

This study was based on the analysis of 59 cases Criteria for the diagnosis of acute hyperparathyroidism were· surgically confirmed primary hyperparathyroidism with serum calcium levels $\geq$3·75 mmol/l (150 mg/l) and more than one severe clinical sign Forty per cent of the patients were considered critical at the time of admission. Ten patients with serum calcium levels $\geq$3·75 mmol/l, but without severe clinical signs, were excluded from the study.

Results

Forty-five women and 14 men with a mean age of 58 years (range 27–87 years) were included in this study. In 36 cases (61 per cent), primary hyperparathyroidism was discovered only after admission for an acute episode. Five patients (8 per cent) had known and documented hyperparathyroidism before admission. Twenty-one patients (36 per cent) had a typical but neglected past history of primary hyperparathyroidism. The incidence of clinical signs indicating the severity of hyperparathyroidism was very variable (*Table 1*). All patients had at least three severe signs, in various combinations, the most frequent signs being muscular weakness, an altered state of consciousness and dehydration. The time between the first appearance of symptoms of a high serum calcium and its clinical confirmation varied from a few days to several months. Since 1978, the measurement of serum calcium has become routine in hospitals, and the delay in diagnosis has become much less.

Serum calcium levels ranged from 3·75 to 5·62 mmol/l (150–224 mg/l; *Figure 1*). In 12 per cent of patients, serum calcium levels had been >4 mmol/l over a period of several months Serum phosphate levels ranged from 0 20 to 1·22 mmol/l; 53 per cent of patients had no evidence of low serum phosphate. Serum parathyroid hormone level was determined in 48 patients, but was known before surgery in only 32 cases. In all cases, the hormone levels were very high (4–30 times the normal).

Treatment before surgery

Before admission to our department, 56 patients received medical treatment in order to lower serum calcium levels. Six patients required only rehydration to re-establish normal electrolyte status. Fifty patients were treated with hypocalcaemic agents (frusemide, mithramycin, oral diphosphonates). The efficacy of the various treatments was difficult to assess as each one was administered at different dosages and in varying combinations. These drugs were always effective, and no complications occurred with frusemide and diphosphonates. By contrast, in 30 per cent of cases, reversible hepatic and haematological abnormalities were observed when mithramycin was included in the treatment. There was no evidence of combined drugs being more effective than single drug therapy When drug treatment was effective the benefit was transient. Two patients with serum calcium levels >5·50 mmol/l (220 mg/l) underwent haemodialysis, which resulted in an effective decrease of calcium levels to 3·00 mmol/l (120 mg/l) However in both cases levels rose threateningly within a few hours of dialysis.

Immediately after admission to our surgical unit, all 59 patients were rehydrated and electrolyte normality was re-established (with forced diuresis, when necessary) using frusemide Mithramycin was given to five patients. Forty-four patients (75 per cent) underwent surgery within 48 h of admission, 12 patients (20 per cent) between day 2 and day 8, and three patients (5 per cent) on day 10. Surgery was delayed for the latter 15 patients to allow treatment for concomitant diseases (diabetes, heart and respiratory failure), and in five cases to investigate the hypercalcaemia. Rapid volume replacement was instituted if hypovolaemic shock was predominant, followed by infusion of isotonic or hypotonic solution according to the type of dehydration. Infusion volumes were sometimes very high and involved careful monitoring of the central venous pressure. Most of the patients required only rehydration, which produced a fall in serum calcium levels to below 3 22 mmol/l (130 mg/l) in 14 patients Forty-five patients had forced diuresis with 40–100 mg frusemide intravenously. This treatment was started after dehydration had been treated and slight volume expansion achieved. Losses, which may be considerable (1–2 litres per hour of sodium-rich and potassium-rich urine), were assessed by means of hourly urine volume and electrolyte measurement Frusemide infusions were repeated whenever the hourly urine volume was <500 ml. Infusion fluids consisted of isotonic glucose with the addition of small amounts of sodium

Table 1 *Frequency of severe clinical signs in 59 patients with acute primary hyperparathyroidism*

Clinical sign	%
Severe weakness	88
Altered states of consciousness	65
Severe dehydration	65
Rapid weight loss	60
Vomiting	30
Coma	7
Acute pancreatitis	4

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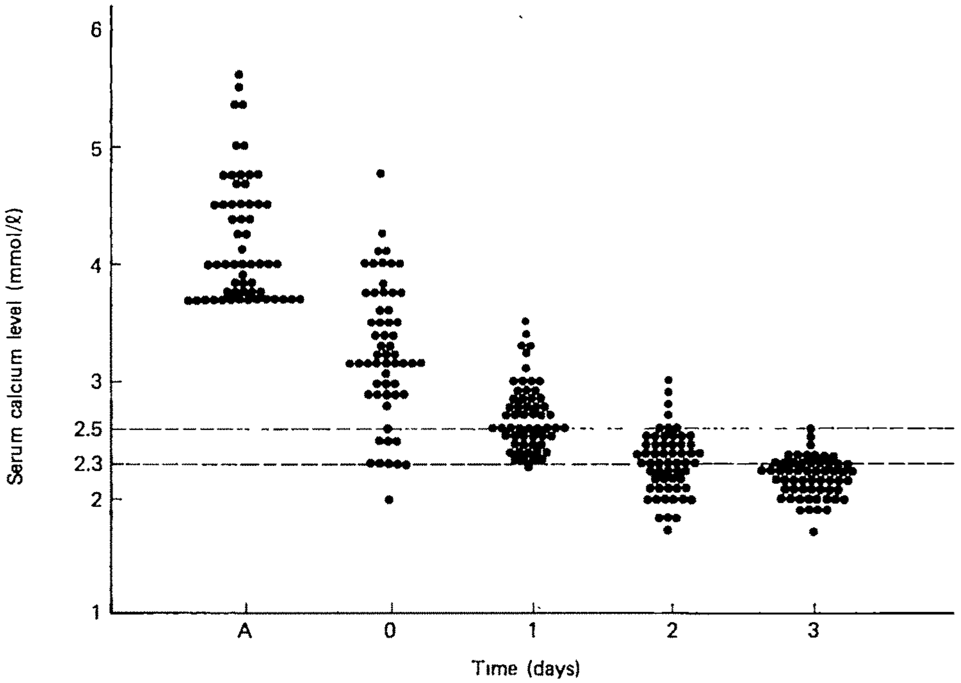

Figure 1 *Preoperative and postoperative serum calcium levels of 59 patients with acute primary hyperparathyroidism. A, First day of medical treatment; 0, operative day; ----, normal serum calcium level limits (2·3–2·5 mmol/l)*

chloride and potassium, equal to urinary losses. Magnesium sulphate was given orally. All patients who underwent surgery were fully hydrated and in optimal electrolytic and physical condition. Only ten patients had serum calcium levels within normal limits or hypocalcaemia at the time of surgery (day 0); 38 patients had serum calcium levels above 3·22 mmol/l, and 15 patients maintained a level ≥3·75 mmol/l (*Figure 1*).

Surgery

Surgery was performed under general anaesthesia by experienced parathyroid surgeons. Two patients had already undergone an unsuccessful neck operation in another hospital. Cervical exploration was performed in all patients regardless of the results of parathyroid localization investigations. When the pathological parathyroid lesion was located, the other glands were routinely sought. Parathyroid lesions were found during cervical exploration in 57 patients. The lesion was located in the lower mediastinum in the other two patients and sternotomy was necessary, the first case immediately after the neck exploration and the second case 7 days later.

The parathyroid lesions were as follows: parathyroid adenoma (55 cases), primary hyperplasia of four parathyroid glands (two cases) and parathyroid cancer (two cases). Severe hypercalcaemia was caused mainly by large lesions (2–5 g), although much smaller lesions were found. Histology revealed recent haemorrhagic necrosis and cystic areas in 60 per cent of adenomas. Overall, results were striking: serum calcium levels returned to normal within 24–48 h and, above all, there was almost immediate recovery of consciousness and disappearance of any existing abdominal and bone pain.

None of the patients died before surgery. Three patients had recurrent nerve paralysis; in one of these cases, the nerve was cut intentionally during the excision of a parathyroid cancer. During the postsurgery period, three patients had very low serum magnesium levels, induced by forced uncompensated diuresis and revealed by gradually increasing mental confusion, which regressed rapidly following administration of magnesium phosphate. After surgery, 21 patients were hypocalcaemic with distal tingling, but there were no cases of severe tetany Myocardial ischaemia occurred in two patients and pulmonary infection in one. One patient died of pulmonary infection 2 months after surgery.

Discussion

Acute hyperparathyroidism is rare. Its incidence in primary hyperparathyroidism varies from 5 to 10 per cent depending on the study[1–3]. Its incidence is increasing, not because of an increased prevalence of acute hyperparathyroidism but because calcium measurement in hospital patients is now routine[4].

The clinical signs of acute hyperparathyroidism in this study were similar to those previously reported[3]. In most cases, the acute episode revealed the underlying disease. However, it is important to note that a third of our patients had had typical, but neglected, signs of hyperparathyroidism for several months and even years before diagnosis[5]. There was not a predictable correlation between the high level of serum calcium and clinical severity, particularly in relation to disordered consciousness[6]. One of the patients was followed up after he refused surgery. His calcium was >4 mmol/l (160 mg/l) but he had no neurological disorder. In our study involving 1000 cases of primary hyperparathyroidism, several patients showed no serious symptoms in spite of calcium levels >3·75 mmol/l (150 mg/l).

In most cases, 1 or 2 days should be enough to assess severe hypercalcaemia and make an accurate diagnosis[3,4,6–9]. Such investigation generally helps to identify other causes of high serum calcium. The diagnosis of acute hyperparathyroidism was rejected 13 times in this series. In doubtful cases suppression of the hypercalcaemia after administration of steroid will exclude sarcoidosis and malignancy. Vitamin D intoxication is usually reported during questions on past history. However, this went unnoticed in one patient who underwent an emergency operation.

In doubtful cases, surgery must be carried out even when the cause of the hypercalcaemia is in doubt; one of our patients had myeloma[8] and another had retroperitoneal leiomyosarcoma, and both were associated with acute primary hyperparathyroidism. We believe it is preferable to carry out a negative cervical exploration than to leave in place an adenoma inducing acute hyperparathyroidism. No mortality was reported in the nine patients who underwent surgery after erroneous diagnosis.

Only surgery can provide proper treatment of acute hyperparathyroidism. Medical treatment before surgery is intended to provide rehydration, to correct electrolyte disorders, and to lower serum calcium to less dangerous levels. However, it is not necessary to obtain normal levels, and surgery must be carried out as soon as the patient's clinical condition and metabolism improve sufficiently. Even if there is no clinical improvement, particularly with regard to consciousness, after several hours of medical treatment, patients should rapidly undergo surgery[6,7]. We consider that this policy accounts for the low mortality rate in this series, whereas the mortality rate exceeds 30 per cent when medical treatment is extended[4,9,10]. Cervical exploration must be performed by experienced surgeons Although in the majority of cases the adenomas are voluminous, exposure of all four glands is essential, especially when the lesion seems small in proportion to the serum calcium level. Two of our patients had primary hyperplasia. If cervical investigation fails to find a parathyroid lesion, sternotomy must be performed immediately when there is acute hypercalcaemia; this is in contrast to our usual procedure for hyperparathyroidism.

We conclude that acute hyperparathyroidism can be reliably and confidently treated if prompt resuscitation is followed by urgent surgery.

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The development and evaluation of a clinical test of surgical resident proficiency

Benjamin O. Anderson, MD, John H. Sun, MD, Ernest E. Moore, MD,
Laetitia L. Thompson, PhD, Alden H. Harkin, MD, *and* **Edward J. Bartle, MD,**
Denver, Colo.

The two purposes of this study were to develop a clinical test of surgical resident proficiency and to compare this clinical test with currently applied methods of resident evaluation. Appendicitis is a common surgical disease, and its accurate diagnosis depends largely on clinical acumen. Ten third-year surgical residents prospectively evaluated 107 patients admitted because of suspected appendicitis. After taking a history, performing a physical examination, and reviewing laboratory data, these residents were asked to state, as a percentage, the likelihood that each patient had appendicitis. Sixty-three patients had appendicitis documented by pathologic inspection after appendectomy. Forty-four patients did not have appendicitis, as was determined by operation (17) or by in-house observation and resolution of abdominal pain (27). These outcomes were used to calculate a diagnostic ability score (DAS) for each resident. Residents were evaluated by standard methods including in-service examinations and monthly evaluations by the attending staff. Residents were also evaluated by nonstandard, but potentially useful, neuropsychologic and psychologic tests, including the trail making test, the Ravens progressive matrices test, the paced auditory serial addition test (PASAT), the grooved pegboard test of manual dexterity, and the profile of mood states (POMS) psychologic questionnaire. Cumulative scores were calculated and compared by multiple regression with coefficient variance analysis. The correlation (R^2) of DAS with standard evaluation techniques was as follows: In-service (0.055), faculty (0.508), trails (−0.293), Ravens (0.028), PASAT (0.251), dexterity (0.432), POMS (0.381). We found that (1) the DAS is a discriminating clinical test; (2) the DAS correlates with subjective faculty evaluation; and (3) the DAS does not correlate with in-service examination scores. We conclude that faculty evaluation remains the best currently applied test of surgical resident clinical proficiency as measured by the DAS. (SURGERY 1989;106:347-53.)

From the Departments of Surgery and Psychiatry, University of Colorado Health Sciences Center, Denver, Colo.

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METHODS

Resident group. Admitting surgical residents at Denver General Hospital and the University of Colorado Hospital were asked to participate in this study from February 1986 to December 1987. In the normal course of their duties, these third-year residents evalu-

Presented at the Fiftieth Annual Meeting of the Society of University Surgeons, Baltimore, Md, Feb 9-11, 1989

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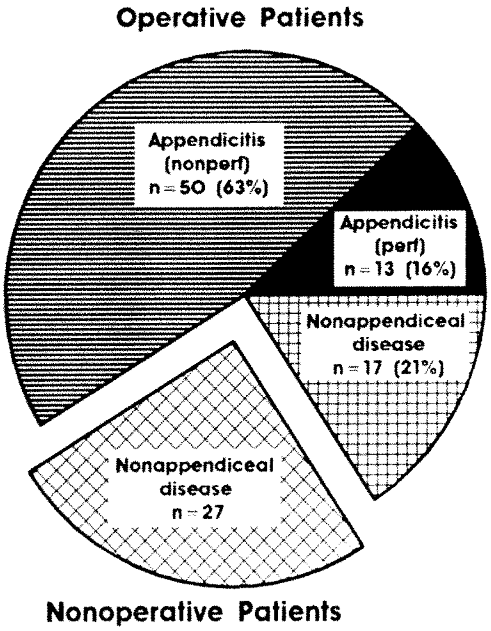

Fig. 1. Distribution of patients by operative status and final diagnosis. Operative patients were diagnosed with appendicitis or nonappendiceal disease on the basis of their pathologic reports. Nonoperative patients had complete symptomatic resolution and were assumed to have nonappendiceal disease.

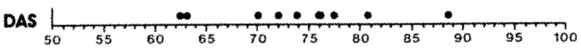

Fig. 2. Distribution of diagnostic ability scores among 10 surgical residents. The DAS is a discriminating clinical test based on the diagnosis of appendicitis.

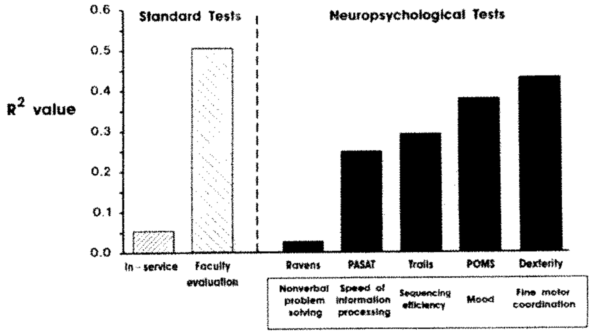

Fig. 3. Correlations between DAS and currently applied measures of resident ability. The strength of linear association between the DAS and other tests was measured by R^2 values, calculated from the Pearson correlation coefficient *(R)*. The DAS correlated most strongly with faculty evaluation and intermediately with neuropsychologic tests. The DAS did not correlate with the in-service examination.

vidual scores were independently correlated with the DAS, and the best R^2 value of the group was reported. Lastly, R^2 values less than 0.30 were interpreted to indicate that there was no correlation between the two variables being compared.

RESULTS

Fourteen surgical residents evaluated 115 patients for possible appendicitis. These residents had similar degrees of experience with appendicitis, each having seen a minimum of 20 cases before initiation of the study. Four residents who entered three or fewer patients were eliminated from analysis because their data pools were thought to be too small to be meaningful. The 10 remaining residents evaluated 107 patients, forming the data base for this study (Fig. 1). Of these 107, 63 patients (59% of the total population) were found to have appendicitis at laparotomy (50 nonperforated, 13 perforated). Seventeen patients were found to have nonappendiceal disease at operation (16 laparotomies, one laparoscopy). Three of the 16 laparotomy patients with nonappendiceal disease had other problems warranting surgical attention (perforated Meckel's diverticulum, perforated cecal ulcer, bowel obstruction from adhesions). For DAS calculation, the Meckel's diverticulum and cecal ulcer patients were counted as appendicitis patients to avoid penalizing residents for essentially correct diagnoses. The remaining 13 operative patients had nontherapeutic laparotomies (16% of the operative group). Ten of the 13 were women in the child-bearing years. The 27 nonoperative patients were observed and discharged after resolution of their symptoms. None returned with further complaints of abdominal pain.

Diagnostic ability scores were calculated for each resident and ranged from 62.4 to 88.6, with a mean of 74.0 and a standard deviation of 7.8 (Fig. 2). The DAS was correlated with other tests by linear regression and the calculated R^2 values were compared (Fig. 3). Faculty evaluations correlated best with the DAS ($R^2 = 0.508$), and in-service examination scores did not correlate with the DAS (Fig. 4). Less than 6% of the variation in in-service scores among residents could be attributed to a linear relationship between those scores and the DAS. Among the neuropsychologic and psychologic tests, the scores correlating best with the DAS were the dominant hand score of the grooved pegboard dexterity test ($R^2 = 0.432$) and the confusion score of the POMS psychologic questionnaire ($R^2 = 0.381$).

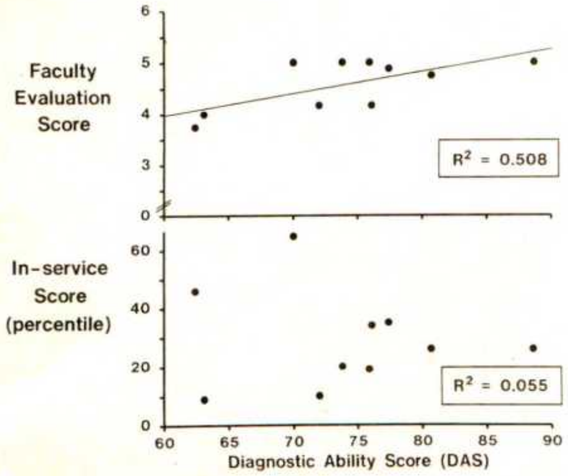

Fig. 4. Relationships between DAS and faculty evaluation (above) and in-service examination (below). Resident scores are represented by points with DAS on the x-axis and faculty evaluation/in-service examination scores on the y-axes. DAS correlated with faculty evaluation and did not correlate with in-service examination scores.

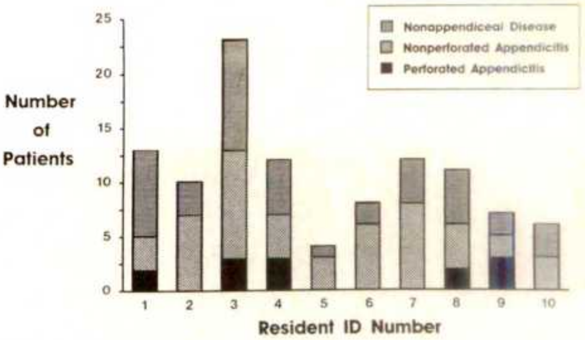

Fig. 5. Characteristics of patient subgroups evaluated by different residents. Patient subgroups varied in the total number of patients, the percentage of patients with appendicitis, and the percentage of appendicitis patients with perforation. Subgroups also varied in the percentage of female patients (not illustrated here).

The remaining neuropsychologic tests did not correlate with the DAS. No written test correlated with the DAS as strongly as faculty evaluation.

Because each resident evaluated a different subgroup of patients, characteristics of the patient subgroups were correlated with the DAS to determine whether scores were biased by patient sampling. As illustrated in Fig. 5, patient subgroups varied in the total number of patients (ranging from 4 to 23), the percentage of female patients (ranging from 25% to 73%), the percentage of patients demonstrated to have appendicitis (ranging from 38% to 78%), and the percentage of appendicitis patients demonstrated to have perforation (ranging from none to 60%). Each of these characteristics was correlated with the DAS, and R^2 values were calculated (Fig. 6). The total number of patients, the percentage of female patients, and the percentage of appendicitis patients with perforation did not correlate with the DAS ($R^2 = 0.269$, 0.051, and 0.075, respectively). The percentage of patients with appendicitis (perforated and nonperforated combined) did correlate with the DAS (Fig. 7), but the degree of correlation was marginal ($R^2 = 0.311$). No characteristic that varied among patient subgroups correlated with the DAS as strongly as did faculty evaluations ($R^2 = 0.508$).

The degree of correlation between faculty evaluation and the DAS was enhanced in the subset of residents who evaluated the most patients. For the entire group of 10 residents, the degree of correlation ($R^2 = 0.508$) was significant by the t test at the $p < 0.05$ level ($t = 2.87$). For the six residents who evaluated 10 or more patients, the degree of correlation was increased ($R^2 = 0.808$), which is significant at the $p < 0.02$ level ($t = 4.10$). For these six residents there was still no correlation between in-service scores and the DAS ($R^2 = 0.001$), and the degrees of correlation between neuropsychologic test scores and the DAS were relatively unchanged.

COMMENTS

Appendicitis is a common surgical problem, and its diagnosis depends largely on clinical acumen. Despite technologic developments, no major improvement in the preoperative diagnosis of appendicitis has been made in the past 30 years.[5] Individual diagnostic studies, such as barium enema and ultrasonography, and laboratory tests, such as white blood cell count with differential, have been scrutinized for their ability to distinguish appendicitis from nonappendiceal disease.[6-8] Other authors have devised scoring systems based on history and laboratory findings to aid in the diagnosis of appendicitis.[9, 10] Most experts agree, however, that no single finding defines the diagnosis of appendicitis,[11, 12] and advanced diagnostic tools are, at best, an adjunct to the clinician's subjective decision-making process, which is based largely on personal experience and ability to integrate data.[13] The diagnosis of appendicitis, then, is a reasonable clinical problem for the assessment of clinical profiency among residents at similar levels of training.

A test of clinical proficiency (DAS) was created for this study on the basis of residents' confidence and

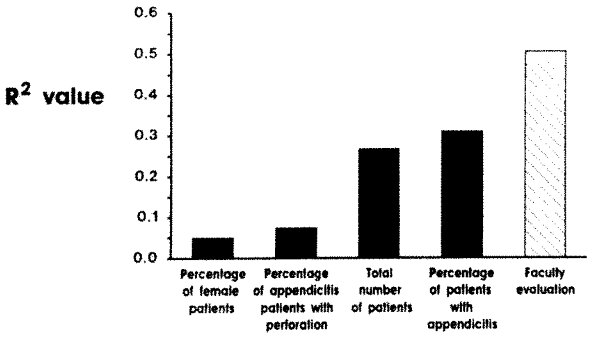

Fig. 6. Correlations between DAS and characteristics that varied among patient subgroups evaluated by different residents. No patient subgroup characteristic correlated with DAS as strongly as did faculty evaluation.

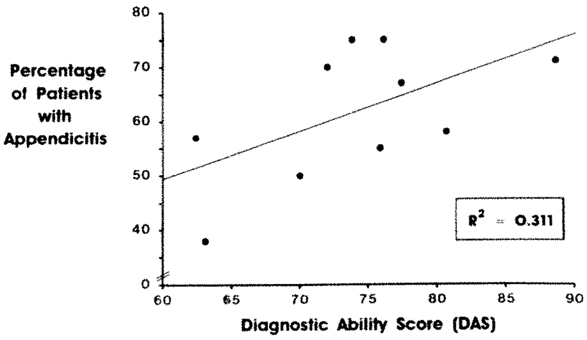

Fig. 7. Relationship between DAS and percentage of patients demonstrated to have appendicitis (perforated and nonperforated appendicitis combined). Residents who evaluated a greater percentage of patients with appendicitis tended to score more highly on the DAS.

accuracy in the diagnosis of appendicitis as verified by clinical outcome. This outcome was determined by the pathologist to be appendicitis or nonappendiceal disease for operative patients, but was assumed to be nonappendiceal disease for nonoperative, spontaneously recovered patients. This assumption may not be true in every case. Occasional pathologic reports describe cellular changes consistent with resolving appendiceal inflammation,[12] indicating that acute appendicitis does not invariably progress to perforation. Such changes were noted in one of the 87 pathologic reports reviewed for this study. The existences of recurrent and chronic appendicitis also suggest that appendicitis can spontaneously resolve. These entities, however, have incidences of, at most, 10% and 1.5%, respectively.[14] The spontaneous resolution of acute appendicitis appears to be an uncommon event and probably does not significantly affect the accuracy of the DAS.

The DAS was found to be a discriminating clinical test. Residents reported varying degrees of certainty in their diagnoses of appendicitis and nonappendiceal disease that, when averaged, resulted in a spectrum of DAS scores. Factors potentially contributing to this variation in scores other than diagnostic ability were controlled within practical constraints. Extensive prior experience with the diagnosis of appendicitis presumably improves a resident's diagnostic confidence and accuracy. As a result, residents at the same level of clinical training were selected for analysis. Differences among patient subgroups seen by different residents could also alter overall scores because some patients' conditions may be more easily diagnosed than others. For this reason, residents who entered fewer than four patients into the study were eliminated from analysis. Characteristics that varied among the remaining patient subgroups were then correlated with the DAS to determine if an overt differences among subgroups biased the resulting scores. Only the percentage of patients with appendicitis correlated with the DAS, and the degree of this correlation was marginal ($R^2 = 0.311$). This indicates that appendicitis may be, on the whole, easier to confidently diagnose than nonappendiceal disease. This result might have been anticipated because appendicitis patients tend to exhibit more obvious signs and symptoms as their disease progresses toward perforation. It would appear that the variation in DAS scores among residents reflects a true difference in diagnostic confidence and accuracy for appendicitis and is, at most, marginally affected by other factors.

The commonly accepted premise that diagnostic accuracy improves as more patients are seen could not be verified in this study. The number of patients in subgroups evaluated by different residents failed to correlate with the DAS, indicating that residents who evaluated more patients did not necessarily have higher DAS scores. (It would be interesting to repeat this study using the same residents in later years of training to determine if the DAS improves in subsequent stages of clinical development.) Despite its lack of correlation with the DAS, the number of patients evaluated by individual residents remains an important consideration. The validity of the DAS as a measure of diagnostic ability hinges on each resident's evaluating a sufficient number of patients to adequately sample his or her clinical skill. A minimum of four patients was arbitrarily selected for DAS calculation, but a higher minimum would presumably increase the validity of the scores. For this reason, statistical analyses were repeated using the subset of six residents who evaluated 10 or more patients, and it was verified that the observed correlations for the entire group of 10 residents persisted for the more select group.

SUMMARY

The DAS was developed as a clinical test of resident proficiency and was compared with currently applied methods of resident evaluation. The DAS correlated with faculty evaluations but did not correlate with in-service examination scores. Neuropsychologic and psychologic test scores either did not correlate with the DAS or correlated less strongly with the DAS than did faculty evaluation. When the same statistical analyses were performed using the test scores of the six residents who evaluated 10 or more patients, the same findings were observed. Furthermore, the level of significance of correlation between faculty evaluation and the DAS was enhanced from $p < 0.05$ to $p < 0.02$. We conclude that subjective faculty evaluation remains the best currently applied test of surgical resident clinical proficiency as measured by the DAS.

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Correspondence

Anergy in patients with biliary lithiasis

Sir

I was intrigued to read the report regarding 'Anergy in patients with biliary lithiasis' (Cainzos *et al. Br J Surg* 1989, **76**. 169–72) However I feel that their conclusions, that patients with acute gallstone cholecystitis demonstrate evidence of impaired host immunity, are overstated

At this stage it is well recognized that jaundiced (icteric choledocholithiasis in this series) patients are immunosuppressed. This is based on several studies which have examined a number of parameters of immune function in the presence of hyperbilirubinaemia[1,2]. The type of immune dysfunction would appear to depend upon the underlying disease process[3] Patients with obstructive jaundice exhibit impaired lymphocyte responsiveness probably owing at least in part to the suppressive action of the bile salts[4]. This deficiency is also likely to be contributed to by the presence of underlying malignancy in a proportion of cases It is clear from my own studies that the generation of interleukin 2 is also markedly reduced in the presence of jaundice (unpublished data).

However, the evidence with respect to the patients with cholecystitis is rather more sketchy It is generally appreciated that patients with an active inflammatory process such as infection will exhibit impaired cell mediated immunity. I believe that to suggest that the patients with acute cholecystitis represent anything more than simple infected/inflamed cases cannot be sustained Furthermore, there is no reason to think that patients with gallstones are immunosuppressed – because that is the obvious extrapolation of these data

I believe that this paper provides significant contributory data to the field of jaundice and immunity derived from the patients with common duct stones. Beyond that, I believe that the comments related to the patients with acute cholecystitis are not relevant to the area of biliary disease Rather, they represent an example of the totally separate issue of immunity and acute inflammation.

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Authors' reply

Sir

I have read with interest the comments which Dr Monson has made on my paper and I am very grateful because he tries to contribute to the clarification of the complex relationship which exists between hyperbilirubinaemia and the abscence of impaired cell mediated immunity.

However, I think that his letter needs some clarification·

1 In our study, we have not tried to establish which is the ultimate cause that permits us to know why the patients with jaundice present an alteration of cellular immunity. We have simply pointed out a clinical phenomenon which we had already previously described in jaundiced patients with diverse aetiology[1]; but now we want to make it more concrete and detailed by limiting it exclusively to patients with a biliary lithiasis. We obviously know the articles, and their results, that Dr Monson speaks of, but we obviously have no knowledge of his own results because they have still not been published

2. It is obvious to any Doctor that, by definition, acute cholecystitis is an inflammatory and infectious process and that, because of this, delayed cellular immunity can be disturbed However, *Table 4* of our article demonstrated that the cause of this alteration is not due to the infectious or inflammatory process

3 We are surprised that Dr Monson has arrived at the conclusion that the obvious extrapolation of our paper is that the patients with biliary lithiasis are immunosuppressed

The only conclusion that can be drawn is that the patients with choledocholithiasis and jaundice, and those who presented acute cholecystitis, present an alteration of delayed cellular immunity. The other clear conclusion of our study is that patients with simple cholelithiasis have as low a probability of presenting anergy or relative anergy as a control group of absolutely healthy subjects

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1 Cainzos M, Potel J, Puente JL. Anergy in jaundiced patients. *Br J Surg* 1988; **75**· 147–9.

Necrotizing pancreatitis

Sir

McMahon's group have contributed a timely, scientific and practical guide to the treatment of necrotizing pancreatitis (*Br J Surg* 1989, **76**: 465–71). A similar approach has been advocated recently by Howard[1]. We have treated seven patients with a similar initial strategy of non-operative management, delaying surgical debridement until demarcation occurs or until a potentially life-threatening complication develops. The latter was usually indicated by increasing leucocytosis with a decline in renal or hepatic function, i.e the first sign of impending systemic sepsis or multiorgan failure Using a Chevron incision, a mesocolic approach to the pancreatic necrosis, and radical debridement with hemicolectomy if indicated for extension of necrosis to retrocolic fat, reintervention is minimized. In three of our patients only one surgical procedure was required, although drainage of necrotic material continued for up to 60 days. In the other four patients, multiple (mean 3·8) interventions were necessary; this reoperation rate could probably be reduced with the use of an irrigating silicone elastomer drain as described by the Leeds group. Ventilatory support (four patients), haemodialysis (two patients) and prolonged treatment in an intensive care unit were required by our patients, and one patient eventually died from continuing sepsis Only one patient required insulin on recovery, indicating that the necrotic tissue was largely dead adipose tissue Pancreatography some months later often demonstrates a pancreatic duct of relatively normal length and configuration[2].

Two important issues are raised by the success of the Leeds group First, the value of prognostic scoring and preoperative scoring The decision to operate was based on the evolution of contrast-enhanced CT or clinical deterioration; the scoring system appears to have played no role. It is doubtful whether the scoring systems are even of value for comparison of results from different centres because they are indicative of a sick patient rather than a sick pancreas. Only histology can make a diagnosis of necrosis and its anatomical extent Second, the life-threatening events occurring in the progression from pancreatic oedema to necrosis appear to take place in the peripancreatic fat. As yet, the involvement of cytokines, interleukins or similar agents with potent inflammatory activities on the lethal upheavals occurring in this juxtapancreas adipose tissue have not been explored

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Double lumen and quadruple lumen pouches

Sir

Following our recently published prospective randomized trial of double lumen (J) and quadruple lumen pouches (W) (*Br J Surg* 1988, **75** 1008–11), we would like to present the functional results at 12 months following ileostomy closure on the 30 patients detailed in *Table 3* of the original article The data are expressed as the median and approximate 95 per cent confidence intervals[1] Continuous variables in two independent groups were analysed using the Wilcoxon two-sample test. Proportions were compared using a Fisher's exact test Significance was assumed if $P<0·05$ on a two-tailed test

Daytime frequency of defaecation was not significantly different between the 15 J pouch patients. 5(4–6) compared with the 15 W pouch patients. 4(3–6), $P=0·34$ However, night-time defaecation frequency was significantly less in the patients with a W pouch· 1(0–1), compared with the J pouch patients: 1(1–2), $P=0·03$ This was not entirely due to an increased number of patients having to rise at night to defaecate with a J pouch (13/15) compared with those with a W pouch (9/15), $P=0·215$. The number of patients that experienced episodes of fluid soiling per anus of sufficient quantity to necessitate the wearing of a pad was similar in both groups by day J(1/15) *versus* W(2/15); $P=0·96$ and by night· J(4/15) *versus* W(6/15), $P=0·7$.

There were no episodes of incontinence to faeces in any of the 30 patients One patient in each group was unable to defer defaecation for more than 10 min Both of these patients had evidence of active acute pouch inflammation (pouchitis) on sigmoidoscopic and histological criteria The number of patients taking antidiarrhoeal medication was identical in each group (7/15), as was the number of patients able to discriminate flatus from faeces (12/15).

The similarity of overall functional result was illustrated by a functional score (*Table 1*) for J pouch patients of 2(2–4), compared with a score for W pouch patients of 2(0–4); $P=0·77$.

Table 1

	Functional aspect	Score
1	24-h frequency of defaecation >6	1
2.	24-h frequency of defaecation >10	1
3.	Night-time defaecation	1
4	Defer defaecation <10 minutes	1
5.	Nocturnal fluid leakage per anus	1
6	Daytime fluid leakage per anus	1
7	Wearing of pads	1
8	Taking antidiarrhoeal medication	1
9	Incontinence to faeces	1
10	Absence of discrimination between flatus and faeces	1

This brief functional update of 30 patients who had previously been randomized to either J or W pouches has revealed a similar clinical outcome at 12 months to that reported at 4 months following restoration of intestinal continuity The lower nocturnal defaecation frequency in the patients with a W pouch has been described by others[2]; however, we did not subsequently show a difference in the proportion of patients taking antidiarrhoeal medication

Despite an identical method of ileo-anal anastomosis in each group, a greater number of patients with a W pouch experienced both daytime and night-time soiling episodes compared with J pouch patients, although the difference did not achieve statistical significance.

We see no reason, therefore, to alter the conclusion stated following the initial report of the trial.

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1 Gardner MJ, Altman DG Confidence intervals rather than *P* values estimation rather than hypothesis testing. *Br Med J* 1986, **292** 746–50
2 Nicholls RJ, Lubowski DZ Restorative proctocolectomy the four loop (W) reservoir. *Br J Surg* 1987, **74**: 564–6

Stapled ileal J pouch–anal anastomosis

Sir

We are concerned by the message conveyed by Brough and Schofield (*Br J Surg* 1989, **76**: 350–1) regarding the need to evert the rectum to facilitate placement of a distal purse-string suture during the performance of a stapled ileal J pouch–anal anastomosis We believe the technique to be at best unnecessary and at worst exposing the patient to avoidable postoperative sphincter damage Alternative techniques have been described which enable the rectal stump to be cross-stapled[1], so avoiding the use of a purse-string suture completely Indeed, an article in the same edition of *The British Journal of Surgery*[2] details some of the problems associated with purse-string sutures while describing a technique that avoids the use of both an ileal reservoir purse-string suture as well as one around the rectal stump

Ileal reservoir anastomosis at the dentate line has been shown to be associated with inferior functional results compared with anastomosis at the top of the anal canal[3]. The risk of malignant change in the remaining 1 cm of mucosa is small[4] and the grade of inflammation low[5] Clearly this small risk cannot be ignored, however, inspection of the remaining mucosa is facilitated by the use of a long proctoscope or a paediatric sigmoidoscope We do not share the authors' optimism that 'eversion of the rectal stump does not alter anal function' Data are lacking, but Goligher[6] questioned the validity of comparisons made by himself and others using unmatched patient groups with small numbers and multiple uncontrolled variable factors

Martin[7] described a nocturnal soiling rate of less than 5 per cent in 105 patients (age range 8–69 years), all of whom had a mucosal proctectomy performed from the abdominal route The anastomosis was at 1 cm above the dentate line with the ileal reservoir being hand-sutured and the anastomosis performed endoanally.

Although an increased length of follow-up could have accounted for some of the functional improvement, his results are better than those reported from a recent review of the results of nine separate centres[8].

A recent report of a series of 100 patients, all of whom had a rectal eversion technique performed as part of their ileal reservoir procedure[9], ended with the author describing a nocturnal soiling rate of 25 per cent 12 months following ileostomy closure

Details of the incidence of postoperative bladder and sexual disturbances are lacking as are details of manometry technique We would also question whether retention of semisolid porridge reflects the preservation of continence in the early postoperative stage when stool consistency is liquid and the majority of soiling episodes documented have occurred at night[8]

With the recent emphasis on minimal stretching of the anal sphincter[2,3] during ileal reservoir anastomosis to the anal canal, we feel that eversion of the rectal stump exposes patients to the risk of avoidable complications not only due to excessive sphincter stretch but also to a traction neuropathy of the multiple delicate perirectal autonomic nerves

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1. Adloff M, Arnaud J-P, Thibaud D, Bergamaschi R Facilitating low colorectal anastomosis preliminary results *Am J Surg* 1986, **151** 286–8.
2 Williams NS Stapling technique for pouch–anal anastomosis without the need for purse-string sutures *Br J Surg* 1989, **76** 348–9
3 Johnston D, Holdsworth PJ, Nasmyth DG *et al* Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal proctectomy and endo-anal anastomosis *Br J Surg* 1987, **74** 940–4
4. Kmiot WA, Keighley MRP Totally stapled abdominal restorative proctocolectomy *Br J Surg* 1989, **76** 961–4
5. Deasy JM, Quirke P, Dixon MF *et al.* The surgical importance of the anal transition zone in ulcerative colitis (abstract). *Br J Surg* 1987, **74** 533.
6 Goligher JC Eversion technique for distal mucosal proctectomy in ulcerative colitis a preliminary report *Br J Surg* 1984, **71** 26–8
7 Martin LW Discussion *Ann Surg* 1986, **204** 382
8. Nicholls RJ. Restorative proctocolectomy with various types of reservoir. *World J Surg* 1987, **11** 751–62
9. Becker JM, Raymond JL Ileal pouch–anal anastomosis a single surgeon's experience with 100 consecutive cases *Ann Surg* 1986, **204** 375–81

Book reviews

A Colour Atlas of Extra-anatomic Bypass for Lower Limb Vascular Disease

J. Chamberlain. 265 × 195 mm Pp. 64. Illustrated 1988 London Wolfe Medical Publications Ltd. £19.00.

This volume contains 92 colour illustrations, the vast majority consisting of photographs of various stages of operations to insert axillofemoral and femorofemoral grafts. No extra-anatomical bypass to the legs other than these two procedures is mentioned and while some may be disappointed by the incomplete coverage of the title topic, others will appreciate the concentrated effort made to describe what are, after all, by far the commonest two extra-anatomical operations

The indications and aftercare relevant to the surgery are briefly covered and most space is given to the techniques of graft insertion. Perhaps because this is essentially a 'how I do it' manual, it can appear dogmatic at times, with little attempt to discuss alternatives or grey areas. For instance, only standard Dacron® is used as a graft, without mention of polytetrafluoroethylene, sealed Dacron or externally supported prostheses as possible alternatives. Similarly, routine drainage of vascular surgical wounds is advocated without any indication that this may not be a widespread practice. These are only two of many examples which are all the more significant in a book without references or bibliography Nevertheless, it cannot be denied that the omission of discussion of controversial points allows a clear and concise exposition which some may find attractive.

The most useful role for this book may be as an aid for the surgeon in training who might find its illustrations and commentary helpful when used in conjunction with a more extensive and referenced textbook of vascular surgery.

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Advances in Urology

B. Lytton, W. J. Catalona, L. Lipshultz, E. McGuire. 230 × 160 mm. Pp. 318. Illustrated. 1988. Chicago: Year Book Medical Publishers Incorporated. £35.50.

This is Volume 1 in what I presume will be a series from Yearbook Medical Publishers Incorporated

It consists of a dozen chapters in which authors almost exclusively from the USA give a broad view of their field. A wide variety of subjects are covered with a comprehensive list of recent references at the end of each chapter. The book starts with a chapter from Robert Weiss of Yale on the very difficult subject of the dilated upper urinary tract and is followed by a useful chapter on ultrasound which is likely to become more and more important to the practising urologist once the problem of the interface with the radiologist has been solved. Certainly I believe that urologists in the future will have to be skilled in this extremely useful technique. The place of CT scanning in renal trauma and the more controversial management of carcinoma *in situ* of the bladder with photoradiation therapy are reviewed. Technical chapters include endoscopic treatment of upper urinary tract tumours, microvascular vasectomy reversal and continent urinary diversion with its proliferation of cystoplasties and pouches. Two helpful chapters on the present place of chemotherapy in testicular tumours and another two on the therapy of impotence, including a detailed list of currently available prostheses, are included A short chapter on *in vitro* fertilization as therapy for male infertility seemed an odd choice but the authors claim this was a useful adjuvant to conventional therapy. One major chapter was on extracorporeal shock wave lithotripsy with a brief historical view, clinical results and an appendix in which the second generation lithotripters and their characteristics are mentioned

This is altogether a very useful book for the practising urologist. Every urological department should have a copy and we look forward to future volumes

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Gastroesophageal Reflux

G G. Jamieson and A. Duranceau, 152 × 229 mm. Pp. 281. Illustrated. 1988 Philadelphia. W. B. Saunders. £31.00

I was quite delighted to be asked to review this book as I was just about to buy it for myself and have therefore saved a few pounds It is a mine of useful information about the subject and is creditably up to date, which says something about the efficiency of the publishers. The authors have set out to provide a comprehensive account of relevant physiology, pathology, diagnosis and management. It is extremely well referenced and indexed and will no doubt be cribbed by lots of other writers for years to come. Casual readers will find it easy to dip into in small doses and the more serious will not find it too difficult to read from cover to cover

Far too many books on the oesophagus are thinly disguised symposium proceedings or just readjustments of the thoughts of well known contributors. This one is a welcome exception It should be added to every library and anyone who operates for reflux should actually buy a copy

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An Atlas of Head and Neck Surgery

J. M. Loré. 190 × 267 mm. Pp 1200 Illustrated. 1988. Philadelphia W. B Saunders £85.00.

A generation ago some of us Europeans were privileged to be taught by the American princes of head and neck surgery The first edition of this book was our bible and *vade-mecum* and, indeed, for some of us it was our saviour! It was invaluable for its description of techniques which were not in common use in Europe at that time. It is symptomatic of the change that has come over this surgical subspecialty that this book has grown from 490 pages written by one man to 1200 written by fourteen

All the classical standard procedures are described for benign and malignant disease of the head and neck. However, one wonders if most of the material of the first five chapters (on radiographic anatomy, emergency procedures such as cardiac massage, basic techniques like needle biopsy, endoscopy and simple sinus surgery) have a place in this book. The management of epistaxis and the drainage of abscesses, too, could well have been omitted.

Sadly, much recent material has been omitted· for decompression of the orbit, the excellent exposure provided by an external ethmoidectomy approach is not mentioned, of the approaches to the nasopharynx, much the best, that is via a Le Fort I osteotomy, is not to be found It is surprising to see so much emphasis placed on the use of cervical flaps for reconstruction of the cervical oesophagus, and no mention of the use of revascularized jejunum. The techniques described were abandoned in most large European centres about 20 years ago.

The chapter on flaps contains a good account of the pectoralis major flap, but the rest of this chapter is largely of historical interest only, there being numerous pages on techniques such as the use of the deltopectoral flap, which passed into disuse 10 years ago. The latissimus dorsi flap is not described, and microvascular surgery is dismissed in a few words.

The section on branchial fistulae and branchial cysts is confused and confusing as it is written as if the two were part of the same disease, whereas they are of course entirely different The mythical tract of a branchial cyst is fully described

A section on chemotherapy sits uneasily in this book – as is often the case the views in this chapter are based more on pious hopes than reality. The author states, with respect to adjuvant chemotherapy, that 'Definitive proof of the value of this approach requires carefully controlled studies' Twenty-two controlled trials, covering more than 3500 patients, have now been published. The overall improvement in survival is 3 per cent at the expense of a death rate from toxicity of 7 per cent The author does not mention these facts

Some of the writing is difficult to follow. Of blindness, one author says, 'When it is iatrogenic, it becomes such a sequelae of any surgical procedure that the *axiom primum non nocere* is most pungent ' I wonder what he meant

This book is intended for general surgeons undertaking the occasional foray into the head and neck As such it will continue to be useful as a description of basic and well established excisional techniques Those working in the larger European centres devoted to head and neck surgery will have to turn elsewhere for guidance on many current techniques, particularly in reconstruction

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The Year Book of Vascular Surgery

J. J Bergan and J S T Yao 152 × 241 mm Pp 299 Illustrated. 1988 Chicago. Year Book Medical Publishers Inc £34.00

A yearbook of a surgical specialty, bringing to busy clinicians all that has been considered to be new in publications in their field for the last year, is a delightfully simple concept, and clearly of enormous value However, it is hard to think of any book which is more difficult to compile. Not only must the surgical literature be sifted regularly throughout the year, and interesting papers brought to the attention of the editors, but the editors and their team must then decide how much credence to give these publications which are of enormously variable scientific value and academic reliability The next problem is how much of the paper to publish A bald abstract may give too little information to be of any real interest to the reader, and it is clearly not possible in such a volume to publish the whole paper The authors have achieved an admirable compromise to the dilemma with which they were faced. They present expanded abstracts of their selected papers, most of which are followed by an appropriate editorial comment. The comments are very tactful but reading between their lines, the editorial opinion of the message of the work comes through loud and clear. The selected papers cover a wide spectrum of topics in arterial, venous and lymphatic disease.

Clearly the editors must be concerned that they may have missed valuable publications from their list, but I do not think they have missed many, indeed none that I have noted and would have wished to have seen included Bergan, Yao and their large team of assistant editors must be congratulated on this excellent work which should be essential reading for every surgeon involved in the management of arterial and venous disease

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The Original Bassini Operation for Inguinal Hernia

A Chinaglia. 200 × 275 mm Pp 114. Illustrated 1988 Padua, Italy Piccin Nuova Libreria £22 00.

Bassini is a name well known to European surgeons. Bassini described outcome measurements after operation first, invented an approach to the thyroid, performed acromiothoracic amputation of the upper limb first, resected a femoral aneurysm first, and devised an operation for inguinal hernia. In these offshore European islands, Bassini's operation for inguinal hernia is remembered but rarely performed correctly as Bassini described it Whereas Bassini himself had excellent results from his hernia operation, in England and Ireland nothing but baneful outcomes have followed our local corruptions of Bassini's scrupulous technique (and the concept that underpinned it) The late Professor Alcide Chinaglia was a pupil of Bassini's last Chief Assistant, Professor Penzo. The Bassini heritage is thus passed on to Chinaglia through the University of Padova This beautifully illustrated monograph is the fruit of this inheritance The book is a worthy contribution to the centenary of a great surgeon· Edoardo Bassini, we salute you!

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Microcomputers in Medicine

P D Coleridge and J H Scurr. 165 × 241 mm. Pp 205 Illustrated 1988 Oxford Springer-Verlag £40 00

This book is a series of chapters based on the proceedings of the Fourth Micro-medical Computer Workshop held at the Middlesex Hospital in September 1986 The 11 chapters present the experiences of a number of workers who have developed microcomputers for their own professional uses in a clinical and research environment Two main themes predominate The first one is the use of microcomputers in the development of clinical audit systems, largely on surgical wards, and is partly a reflection of the continuing trend to improved surgical audit throughout the country A number of different systems are described and anybody wishing to venture into using microcomputers for improving data handling within their office would find the experiences and the opinions of the authors helpful in starting their own system The second theme of the book is the sections relating to the development of microcomputer systems to assist in providing clinical services and the development of laboratory research facilities, particularly in vascular laboratories and research projects related to postoperative fatigue and the clinical use of total parenteral nutrition These chapters describe the methodology used for setting up these particular services and again would be of assistance to the newcomer to the field The book might perhaps have been enhanced by a chapter assisting the newcomer to understand the wide choice of computer hardware and software that is available, with some guidelines on how to choose the most appropriate system for his particular use, and also some speculation into the future of computers in the Health Service as the inevitable trend towards resource management The use of computers within the Health Service and the integration of these microcomputer systems into the larger systems could be a crucial aspect of future clinical policy

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A Colour Atlas of Parathyroid Exploration

A Gunn. 265 × 195 mm. Pp 64 Illustrated 1988 London Wolfe Medical Publications Ltd £19.00

This is a delightful addition to the collection of 'Single Surgical Procedures' produced by Wolfe under the general editorial supervision of Professor W Walker. It is a delight because it is eminently readable, written by an enthusiast (whose enthusiasm is transmitted), well illustrated and contains just enough dogma to be tolerable and therefore accepted fully!

Minor criticisms are levelled which could so easily have been avoided: *Figures 18* and *69* and their legends are identical and noticeably so in a book of only 64 pages and 82 illustrations *Figure 70* should have had its units changed to SI units – current surgical trainees might wonder how a patient could survive with a calcium value greater than 15!

Visits to several centres specializing in parathyroid and thyroid surgery demonstrate that inevitable variations in technique occur without obvious influence on successful outcome or cosmetic result Examples might be the need or otherwise to infiltrate the skin with adrenaline before incision, the gradual acceptance of the lack of need of drains or dressings, or the use of absorbable or non-absorbable ligature material I believe the author might allow discussion on these more minor technical matters Less debate would be entertained (and rightly so) on the clear and comprehensive account of the strategy of exploration in hyperparathyroidism (primary or secondary) Emphasis is placed through the text and acknowledgements of the team work involved, while stressing the essential involvement of the surgeon in preoperative and postoperative decisions Corresponding acknowledgement of the necessary interaction with other colleagues is made; for example, the endocrinologist with patients in hypercalcaemic crisis or the radiologist in localization studies before re-exploration.

For those wishing to specialize in endocrine surgery, this book is essential reading before going to theatre to learn from those whose practice includes patients with hyperparathyroidism

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Notices and announcements

21–23 September 1989
Annual General Meeting of the Association of Surgeons in Training
Cardiff, Wales, UK
Information. Mr B. J. Harrison, Department of Surgery, Cardiff Royal Infirmary, Newport Road, Cardiff CF2 1SZ, UK

22–24 September 1989
Association of Colon and Rectal Surgeons of India
Soura Sringar, India
Information. Dr N A. Wani, Organizing Secretary, Room No. 1318, Sher-i-Kashmir Institute of Medical Sciences, Soura Srinagar, India

22–25 September 1989
58th Annual Meeting of the Royal College of Physicians and Surgeons of Canada
Edmonton, Canada
Information: Anna Lee Chabot, Head of the Meetings and Assemblies Section, Office of Fellowship Affairs, The Royal College of Physicians and Surgeons of Canada, 74 Stanley, Ottawa, Canada K1M 1P4

27–29 September 1989
British Society of Gastroenterology Autumn Meeting
Dublin, Ireland
Information: Charles Fletcher, Confrex, P O Box 963, Brighton, East Sussex BN1 6TN, UK

27 September–1 October 1989
2nd International Conference on Gastrointestinal Cancer
Jerusalem, Israel
Information: The Secretariat, 2nd International Conference on Gastrointestinal Cancer, P.O. Box 50006, Tel Aviv 61500, Israel

4–7 October 1989
Principles of Colon and Rectal Surgery
Minneapolis, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast , Minneapolis, Minnesota 55455, USA

15–18 October 1989
38th Annual Meeting of Brazilian Society of Coloproctology
Rio de Janeiro, Brazil
Information: The Chairman, Ronalvo Ribeiro, Avenide Mem de Sá, 197, Rio de Janeiro, Brazil, CEP 20230

15–20 October 1989
American College of Surgeons 1989 Annual Clinical Congress
Atlanta, USA
Information: Sally Garneski or Susan Krasnow, American College of Surgeons, 55 East Erie Street, Chicago, Illinois, USA

15–21 October 1989
Recent Advances in Pancreaticobiliary Surgery
Edinburgh, UK
Information: Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

16–19 October 1989
2nd International Conference on Melanoma
Venice, Italy
Information: General Secretariat, 2nd International Conference on Melanoma, c/o Isituto Nazionale Tumori, Via G Venezian 1, 20133 Milan, Italy

17–20 October 1989
Progress in the Investigation and Management of Venous Problems
London UK
Information: Miss A. Taft, Conference Officer, Vascular Surgery, 10th Floor, QEQM Wing, St Mary's Hospital, London W2 1NY, UK

20 October 1989
Symposium: **Claudicants: where do the Goal Posts Stand?**
Bath, UK
Information: Dr A Chalmers, Consultant Radiologist, Royal United Hospital, Combe Park, Bath BA1 3NG

23–25 October 1989
International Symposium – The Biology and Clinical Applications of Interleukin 2
Sheffield, UK
Information: Robert Rees, Department of Virology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, England, UK

25 October 1989
Pre-operative Clinical Cardiac Examination and ECG are Adequate Pre-Operative Assessment for Arterial Surgery
London, UK
Information: Mr John Wolfe, Vascular Surgery Unit, St Mary's Hospital, Praed Street, London W2 1NY, UK

6–10 November 1989
MR Physicians Seminar: "Magnetic Resonance Imaging; Techniques and Imaging Methodology"
Philadelphia, USA
Information: Janice Ford, CME Coordinator, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia PA 19104, USA

6–10 November 1989
Annual Course in Advanced Hepatobiliary and Pancreatic Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Du Cane Road, London W12 0NN, UK

7–10 November 1989
The Second British Symposium on Total Knee Replacement
Harrogate, UK
Information. Metaphor Conferences and Meetings, 21 Kirklees Close, Farsley, Pudsey, West Yorkshire LS28 5TF, UK

8–11 November 1989
Endocrine and Nonendocrine Producing Tumours 33rd Annual Clinical Conference
Houston, Texas, USA
Information: Office of Conference Services, MD Anderson Cancer Centre, 1515 Holcombe Blvd, Houston, Texas 77030, USA

12–17 November 1989
International College of Surgeons 16th European Federation Congress
Jerusalem, Israel
Information. Professor Arye L Durst, The Secretariat, PO Box 983, Jerusalem, Israel

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information: J P Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

23–24 November 1989
Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland
Dundee, UK
Information: Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

3–9 December 1989
Breast Cancer: New Developments in Biology, Diagnosis and Treatment
UK
Information: Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr Joseph W. C. Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

19–21 January 1990
The 26th Head and Neck Course
Liverpool, UK
Information. Professor P. M. Stell, Dept of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, UK

20–21 January 1989
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

11–13 March 1990
2nd Surgical Masterclass of the Royal College of Surgeons of Edinburgh
Aviemore, UK
Information: Mrs Maureen Webb, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

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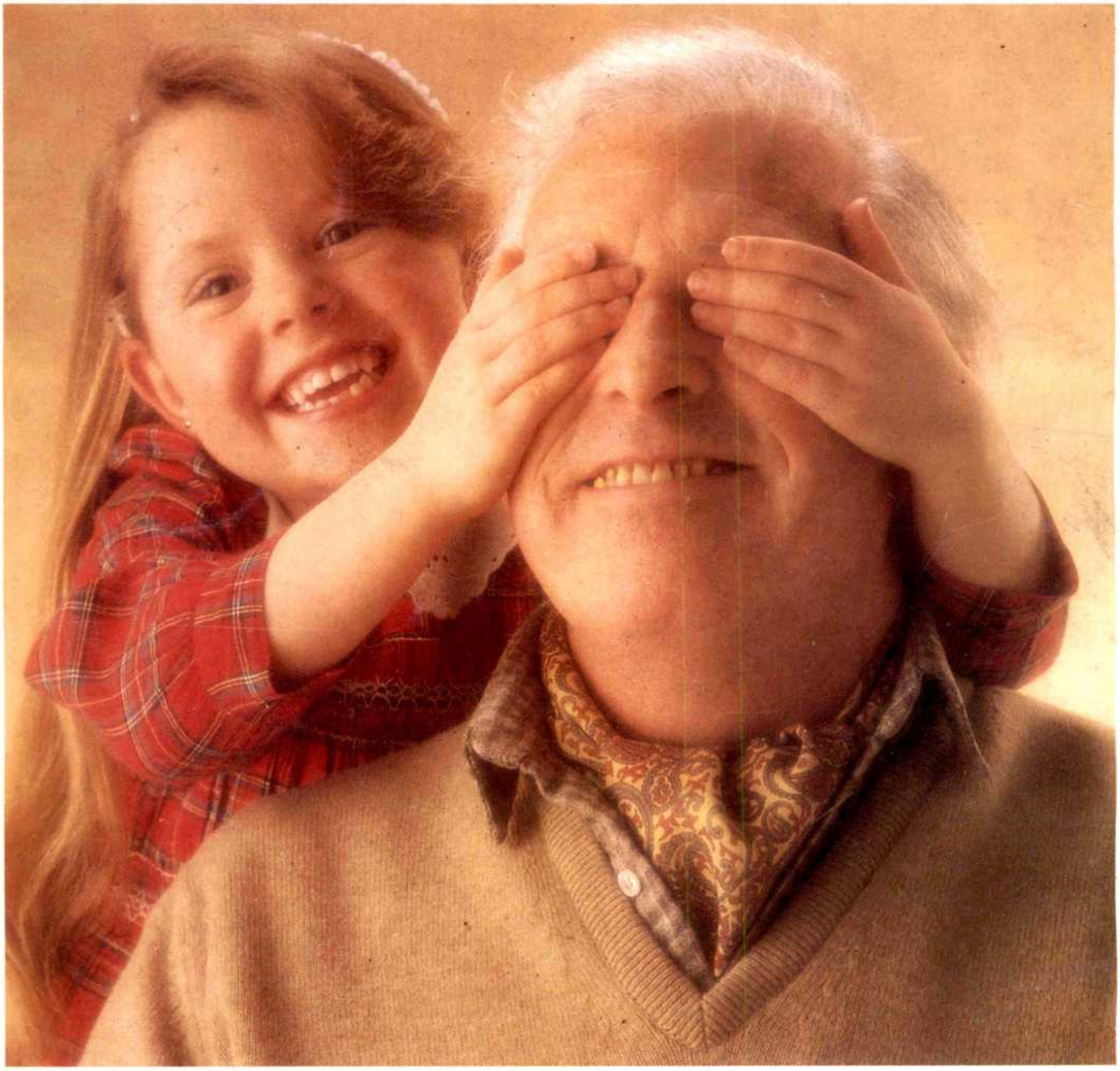

In a recent study[1], 57 prostate cancer patients were invited to participate in choosing their treatment. All were informed that the two treatments available, sub-capsular orchidectomy or 'Zoladex', were similar in efficacy and side effects. 49 of the patients (86%) opted for 'Zoladex'.

A recent trial[2] has established the equivalence of 'Zoladex' to orchidectomy.

Zoladex

goserelin

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Use: Prostate cancer suitable for hormonal manipulation. **Presentation:** A sterile depot containing goserelin 3.6mg. **Dosage and administration:** One depot injected subcutaneously into the anterior abdominal wall every 28 days. **Precautions:** Care with patients at particular risk of developing ureteric obstruction or spinal cord compression. Consider initial use of an anti-androgen at the start of therapy. **Side effects:** Hot flushes, decrease in libido and occasional breast swelling and tenderness. Skin rashes (generally mild). Occasional mild bruising at injection site. Initial transient increase in serum testosterone may cause temporary increase in bone pain. **Product licence number:** 29/0198. **Basic NHS Price:** £114.00 per depot. 'Zoladex' is a trademark. Further information is available from: ICI Pharmaceuticals (UK), Southbank, Alderley Park, Macclesfield, Cheshire SK10 4TF.

Reference 1. Lunglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex'– a new treatment for prostatic cancer. International Congress and Symposium Series.* 125. London: RSM Series, 1987: 47-51.
2. Peeling W B. ibid: 27-46.

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Data Sheet

PDS* and PDS II (Polydioxanone) Sterile Monofilament Synthetic Absorbable Suture

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Presentation

PDS and PDS II (Polydioxanone) Monofilament Synthetic Absorbable Sutures are prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding D & C Blue No. 6 during polymerisation. PDS II (Polydioxanone) sutures are coloured by adding D & C Violet No. 2. PDS II sutures may also be manufactured undyed (clear). PDS and PDS II (Polydioxanone) are available attached to stainless steel needles of various types and sizes, and are sterilised by ethylene oxide gas.

PDS and PDS II (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action: Two important characteristics describe the in-vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass. The general mechanism by which in-vivo degradation of polydioxanone occurs is hydrolysis.

Data obtained from implantation studies in rats show the following absorption profile:

14 days post implantation –
 70% strength remaining
28 days post implantation –
 50% strength remaining
56 days post implantation –
 14% strength remaining

This indicates a significantly longer period of wound support than previously available with an absorbable suture.

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within 180 days.

Uses

PDS and PDS II (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration

By implantation.

Contra-indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required or in conjunction with prosthetic devices e.g. heart valves or synthetic grafts.

The safety and effectiveness of PDS and PDS II (Polydioxanone) sutures in neural and cardiac tissue have not been established.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal epithelium sutures could cause localised irritation if left in place for longer than 10 days. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

Pharmaceutical Precautions

Recommended storage conditions are below 25°C, away from moisture and direct heat. Shelf life is 5 years, the expiry date is shown on each pack. Do not re-sterilise the contents of the pack. Unused product from opened packs should be discarded.

As with all sutures, care should be taken to avoid damage when handling. Avoid the crushing or crimping application of surgical instruments such as needle holders and forceps to the strand, except when grasping the free end of the suture during an instrument tie.

Legal Category

Not applicable.

Package Quantities

PDS is available in various lengths in gauge sizes Metric 0.2 to 0.4 (10/0 to 8/0). PDS II is available in various lengths in gauges sizes Metric 0.5 to 5.0 (7/0 to 2). The sutures are packaged in sealed aluminium foil packs and peel apart overwrap pouches. The sales unit is a film wrapped box containing 12 or 24 packs.

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No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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Irritable Bowel Syndrome
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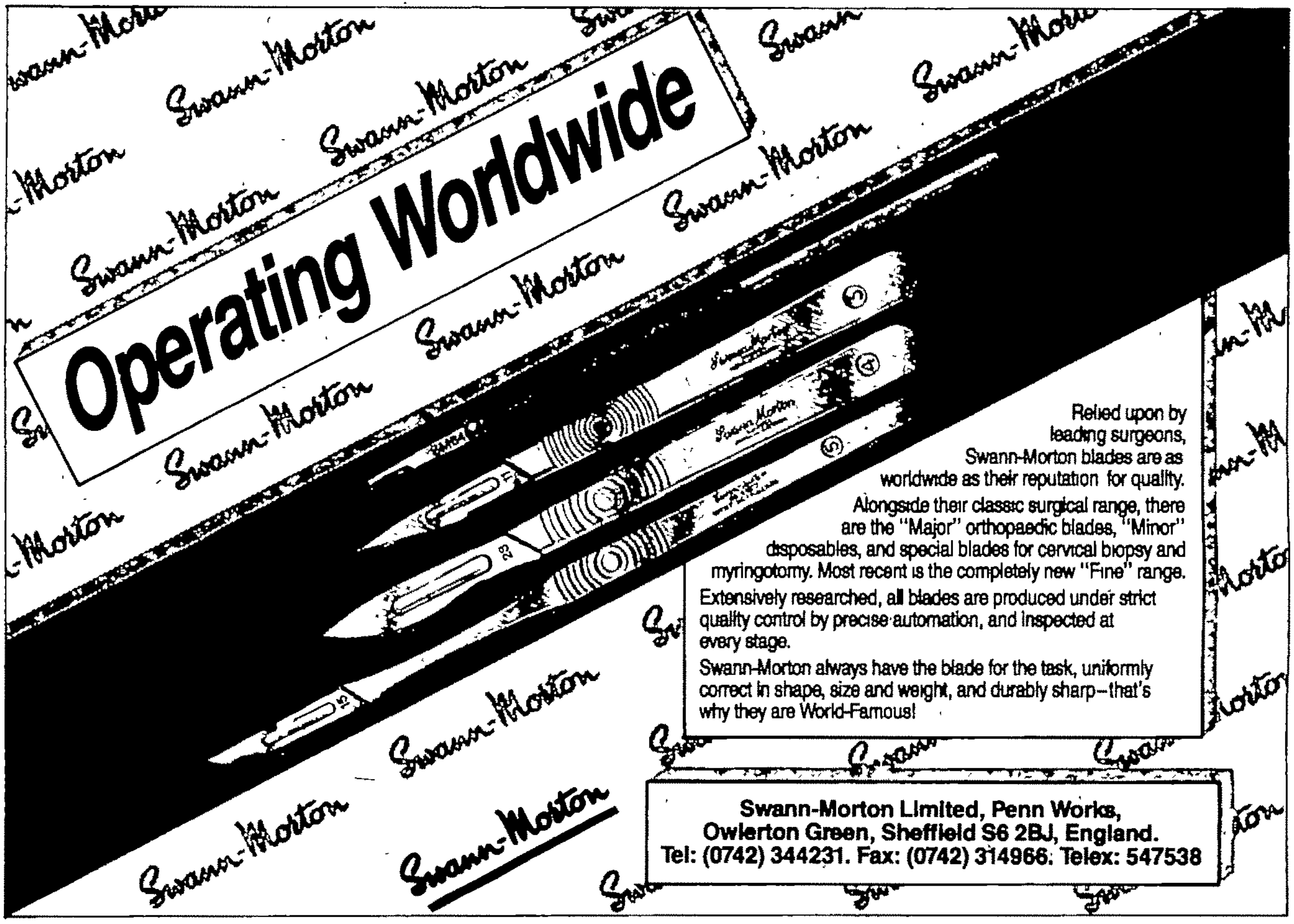

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CONTENTS The supine position • The lithotomy position • The lateral position • The prone position • The sitting position • The transfer of patients and recovery room practice • Specialized positions • Physiological effects of posture in the anaesthetised patient • Index *March 1988 128 pages 246 x 189 mm Softcover 156 line illustrations 0 407 012206 £12 95*

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Br. J. Surg. 1989, Vol. 76, October, 995–996

Barrett's oesophagus

Nearly 40 years have passed since Norman Barrett described in this Journal the condition of *Chronic peptic ulcer of the oesophagus and 'oesophagitis'*[1]. He initially thought that this was a congenital short oesophagus with an intrathoracic stomach, but Allison and Johnstone pointed out that the organ lined by 'gastric' mucous membrane was oesophagus[2]. It is now generally accepted that the columnar-lined oesophagus is the result of long-continued gastro-oesophageal reflux which has denuded the squamous epithelium, allowing the acid resistant gastric-type epithelium to replace it from below, upwards. Two experimental models have shown that the replacement can result from an upwards 'creeping substitution' from the gastric cardia[3] or can result from cells from oesophageal gland ducts[4]. It has also been described following caustic burns and after chemotherapy.

Barrett's oesophagus is not an uncommon condition in children, but is more prevalent in late middle age. In some series a columnar-lined oesophagus is found in 10 per cent of patients with gastro-oesophageal reflux. Gastro-oesophageal reflux appears to be predominantly a western disease and is uncommon in negroid and oriental populations. The condition should be expected when there is a history of long-continued reflux, but in 10–20 per cent of patients there may not be a classical history of reflux. The epithelium is notably unstable, and approximately 60 per cent of patients present with a stricture, 20 per cent with ulceration, 18 per cent with bleeding and 13 per cent with adenocarcinoma. The risk of developing adenocarcinoma, however, has been shown on surveillance studies to be low. Six reports of surveillance results revealed only 11 cases of adenocarcinoma from a total of 456 patients followed for 3–20 years. A population survey in progress has shown that only about one in 20 cases of Barrett's oesophagus in the general population has been diagnosed[5]. Radiologically, a columnar-lined oesophagus should be suspected when there is a high stricture, a long stricture or ulceration in the body of the oesophagus. Endoscopy is essential to make the diagnosis which is confirmed histologically.

Of great significance is the fact that a severe motility disorder accompanies the columnar lining. Whether the motility disorder predates the columnar lining or whether it results from reflux damage is still debated. However, Zaninotto *et al.*[6] have suggested that there is progressive deterioration of function when comparisons are made between normal individuals and patients with uncomplicated reflux or stricture or columnar-lined oesophagus. In Barrett's oesophagus, there was the greatest prevalence of a mechanically defective lower oesophageal sphincter, interrupted swallow responses, and simultaneous contractions in the oesophageal body. The loss of propagating waves is probably due to neural damage, and whether this is the direct result of reflux has yet to be proved. This damage appears to be irreversible because it is not corrected by medical or surgical therapy.

Physician gastroenterologists and surgeons have opposing views regarding the management of the columnar-lined oesophagus. The efficacy of medical treatment has increased remarkably since the advent of the H_2-receptor blocking drugs, omeprazole, and prokinetic agents, and there are now reports of more successful control for up to 6 years. These patients must, however, continue therapy for life and their life-span may be restricted by the fact that there is no available medical treatment to reverse a mechanically defective sphincter. Of 18 patients in the author's series who were treated medically on standard doses of H_2-receptor blocking drugs and prokinetic agents, progression of the columnar lining was documented in 14 of these patients during a surveillance period of up to 6 years. Recent reports from other centres also suggest a failure of H_2-receptor blockade and double doses are advocated.

Surgery, at best, will effectively prevent reflux in some 90 per cent of patients followed for 10 years. There are no reports of progression of the columnar segment, reulceration or stricturing following surgery. There is however no proof that either medical or surgical treatment will prevent adenocarcinoma, and further data are required to resolve this important issue. There are also no comparative prospective studies on the effect of medical or surgical treatment on subsequent life-style. Repeated

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prospective monitoring of oesophageal function in patients with a columnar-lined oesophagus who are treated medically or surgically is necessary to test the efficacy of such treatments. If there is progressive irreversible deterioration of motility owing to gastro-oesophageal reflux, there would be a firm case for earlier surgery in Barrett's oesophagus. Physicians and surgeons should therefore enter into prospective studies and surveillance of all patients with gastro-oesophageal reflux in an effort to establish whether their own respective treatments influence progression.

There is also evidence to support the concept that the complications seen in the columnar-lined oesophagus are related to 'alkaline' reflux. In complicated Barrett's oesophagus there is an increased exposure to an alkaline pH (Reference 7). Whether the irritant agent in the alkaline reflux is bile or pancreatic juice is also not defined. There is as yet no effective medical treatment for alkaline reflux. The need for surveillance of the columnar-lined oesophagus has also been questioned in the light of the low return, in terms of cancer detection, in four series[8], but the concensus view is to continue these studies until more definite guidance can be given. Biopsy evidence of severe dysplasia has indicated the high probability of an associated invasive cancer and the need for resection, but in the two studies reported there were only ten cases with dysplasia of this severity[9,10]. Nine of these patients underwent oesophageal resection and invasive cancer was present in six of the specimens examined. The Organisation for International Studies of Diseases of the Oesophagus (OESO) has recently launched an international collaborative study in an effort to answer some of these questions[11] and the study should be supported and encouraged.

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Br. J. Surg. 1989, Vol. 76, October, 997–998

Malignant melanoma: a plague of our times

Malignant melanoma, the most malignant of skin cancers, has doubled in incidence in the last 10 years, and fourfold increases in a decade have been reported in some patient groups[1]. World-wide statistics demonstrate an average rise in incidence of 7 per cent a year. To put this in perspective, a rising incidence of this nature in Scandinavia would lead to malignant melanoma becoming more common than breast cancer by the year 2000[2]. Although many factors are at play in this phenomenon, there seems little doubt that changes in today's society are largely responsible. Increasing exposure to high intensity sunlight is probably the most telling factor and it seems likely that this has rendered a susceptible fair-skinned, so-called Celtic, population at a much higher risk of developing malignant melanoma than before. However, it should be noted that other factors are important. In Scotland, of 951 melanoma patients, over 50 per cent had never left the UK, even for a brief holiday in continental Europe[3].

The most important prognostic factor in primary cutaneous melanoma is tumour (Breslow) thickness[4] and it is encouraging to learn from the Australian experience and from recent educational programmes in the UK that at least some of the morbidity and mortality may be prevented by excising the primary lesion at an earlier, thinner stage[5]. However, despite the ever-enlarging world experience in the treatment of melanoma patients it is noteworthy that controversy rages over just about every other aspect of their management.

Traditional dogma held that the primary lesion should be excised with a healthy 5-cm margin of normal skin. Because of the anatomical distribution of melanomas such a policy frequently necessitated the use of skin grafts and often produced a very unsightly result. Fortunately such teaching has been called into question in recent times. Concern over the radical excision of primary lesions arose from the fact that despite apparently curative removal of the lesion a significant percentage of patients returned with locoregional deposits. Many of the issues concerning the management of the primary lesion were addressed in a leading article in this Journal in 1986[6]. Currently, the consensus seems to suggest that a 3-cm margin of excision is adequate. A recent study even suggests that a mere 1 cm would be sufficient for those lesions less than 2 mm in thickness[7]. It would also appear to be quite safe to obtain any donor skin graft from the ipsilateral limb.

As the regional lymph nodes are the most common site for melanoma metastases considerable attention has been focused on their management. Surgical excision offers the only effective cure and is the best method of locoregional disease control Surgeons are divided between those who advocate excision of only clinically demonstrable metastatic nodes and those who support a policy of mandatory prophylactic lymph node dissection. The latter policy is based on fear of the presence of occult or microscopic metastases. Traditionally, this operation was reserved for extremity melanomas with lymph node drainage to a single group of nodes. However, some workers have even suggested that some trunk primaries are amenable to lymph node dissection as long as no more than two nodal groups are draining the primary lesion. The opposing viewpoint to this rather aggressive stance is the one that holds that the available evidence is increasingly pointing to malignant melanoma being a systemic disease, not unlike breast cancer. Nonetheless, the controversy regarding lymph node dissection has raged for over two decades and centres on two main points of discussion. Firstly, is it possible to identify the subgroup of patients who are at high risk of developing nodal metastases? Secondly, when should the node dissection be performed? Lack of good scientific data has dogged this question from the outset. Indeed, it still remains that only two prospective randomized trials have addressed the value of elective lymph node dissection in stage I melanoma patients[8,9]. Neither of these studies has proved the case satisfactorily. A rational consensus view has been expressed by Balch[10] who suggests that 'physicians will have to ... make their best judgements about the management of regional lymph nodes in an individual patient setting'. Certainly, in view of the worrying level of morbidity associated with lymph node dissection, it would seem unreasonable at this time to subject all stage I patients to this procedure outside the setting of a clinical trial.

Following the successful use of regional isolated perfusion with melphalan for the treatment of unresectable melanoma, the question logically arose about its use in an adjuvant setting for stage I melanoma of the extremity. Can it be used to eliminate microscopic metastatic cells not removed by primary surgery, and does this improve survival? Over the last decade large numbers of patients have been entered into a series

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of trials addressing these questions and to date hard evidence confirming the efficacy of this technique is lacking[11,12]. Differences in subgroup randomization and distribution in the published studies have rendered interpretation of the data difficult. In addition, in the appraisal of an adjuvant treatment, the added risks and burden to the patient are important factors that must be weighed against the expected gains. To an even greater extent than is the case with elective lymph node dissection, the role of isolated perfusion is in doubt. Toxicity is significant, as is functional limb impairment, limb loss and even death. It would seem reasonable to suggest at this time that this technique should be withheld for those patients with multiple extremity recurrences who cannot easily be treated by surgical excision.

Until such time as public education campaigns have a significant impact on the long-term pick-up of early primary melanoma lesions it seems likely that a considerable number of patients will present for treatment with advanced disease. Attempts to address this subgroup of patients will remain urgent in view of their frequently young age. Regimens of traditional chemotherapeutic agents have consistently proved disappointing with response rates lower than 20 per cent and should probably be avoided because of high levels of toxicity. Immunotherapy has always seemed an attractive proposition owing to the known immunogenic nature of melanomas. It is perhaps in this field more than any other that advances have been made in the last 5 years. The use of interferon and decarbazine suggested the possibility that improved response rates might be attainable. However, it was not until the pioneering work of Rosenberg from the US National Institute of Health began to become available that real progress was demonstrable[13]. Increased response rates are now being achieved utilizing various regimens of interleukin 2, interferon, cyclophosphamide and lymphokine activated killer cells. More recently the combination of reinfused autologous tumour infiltrating lymphocytes and high-dose interleukin 2 has achieved partial responses in some 60 per cent of cases. Although these therapies have yet to be subjected to the rigour of randomized clinical trials, the available results do suggest that immunotherapy represents a genuine advance. Perhaps the advances achieved in the management of disseminated melanoma may provide a clue to a more logical adjuvant therapy for stage I disease.

Sad though it may seem, the practical management of patients with malignant melanoma may have turned full circle. The primary lesion should be excised with a reasonably clear margin, and grafted if necessary. The regional lymph nodes should probably be left alone unless they are clinically involved when block dissection seems to offer the best chance of control. Isolated limb perfusion almost certainly should not be employed outside the current clinical trials. Finally, the management of advanced disease may be about to turn some sort of a corner in the next 5 years, and it may best be approached immunologically. Through a better understanding of adoptive immunotherapy in these cases we may see light at the end of the tunnel in our management of 'earlier disease'.

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A meeting of the Association of Surgeons of Great Britain and Ireland took place in Edinburgh on 29–31 March 1989. The President of the Association, Professor Sir Patrick Forrest, was in the chair.

The Moynihan Prize was awarded to J. L. R. Forsythe, P. M. Dunnigan, G. Proud, T. W. J. Lennard and R. M. R. Taylor for their paper 'Reducing renal injury during transplantation'.

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Reducing renal injury during transplantation

J. L. R. Forsythe*, P. M. Dunnigan, G. Proud, T. W. J. Lennard and R. M. R. Taylor

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Damage sustained by an ischaemic kidney is reduced by cooling the organ. For this reason kidneys are rapidly cooled during the retrieval operation and preserved at low temperature before implantation. When the kidney is removed from cold storage for implantation into the recipient it gradually rewarms (second warm ischaemic time) and a prolonged second warm ischaemic time has been shown to be a cause of acute tubular necrosis following transplantation. The temperature rise in a kidney during implantation has been poorly investigated and little work to minimize that rise has been carried out. This study investigates, in an animal model, the changes that occur in the core temperature of kidneys during the second warm ischaemic time. A jacket has been designed which greatly reduces the rate of kidney rewarming during simulated operative conditions. Kidneys unprotected by the test system showed a rapid rise in temperature from a mean of 1°C to a mean of 20°C after 45 min, compared with those kidneys placed in the protective jacket in which the temperature rose to a mean of only 8°C in the same time. The jacket is not bulky and is simple to use. Maintaining a low kidney core temperature during the second warm ischaemic time will reduce injury to the kidney and should be part of routine clinical practice.

Keywords: Renal transplantation

Cadaveric kidneys sustain damage during retrieval from the donor, during storage, and during implantation into the recipient. However, such damage may be reduced by lowering the temperature of the kidney during each of these events[1]. Renal oxygen consumption falls exponentially with temperature and this is associated with a 1·5–2-fold decrease in enzyme activity for every 10°C drop in temperature[2]. The three major phases of transplantation when renal injury may occur are:

1. *Retrieval:* kidneys are cooled rapidly in the cadaver donor during the retrieval process using a technique known as '*in situ* perfusion'. The aorta is cannulated and cold flushing of the kidneys performed immediately circulation ceases in the donor. This reduces the ischaemic damage during this period, termed the first warm ischaemic time
2. *Preservation:* the second phase is that of preservation during which time the recipient is selected and preparation made for the transplantation operation. It was shown in the 1960s that kidneys could be safely preserved by ice cooling or continuous hypothermic perfusion[3,4]. Both of these systems rely on maintaining the kidney at a low temperature and therefore this phase is called the cold ischaemic time
3. *Implantation:* the final phase of the transplantation procedure is when the kidney is removed from storage and implanted into the recipient. During the time taken to anastomose the renal vein and artery to the recipient vessels the kidney gradually warms and yet is still without a blood supply. This time interval is termed the second warm ischaemic time

The net result of the ischaemic damage which occurs during these three phases may produce acute tubular necrosis in the donor kidney, causing delay in the onset of renal function. Any delayed function has important implications for the transplant recipient who will need dialysis, who will require to stay in hospital longer and in whom the diagnosis of rejection will be more difficult. There is evidence that delay in the onset of graft function adversely affects long term graft survival[5,6]. When cyclosporin A is used that evidence is particularly strong, with one study showing 75 per cent graft survival at 1 year when the onset of graft function is delayed, compared with 91 per cent when immediate function occurs[7]. Recent reports examining the causes of delayed graft function have shown that a long second warm ischaemic time leads to a significantly increased risk of delayed function[8,9]. As it is known that warm ischaemia will severely damage a kidney in 60 min[10] and that

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* *J. L. R. Forsythe is a Wellcome Surgical Fellow.*

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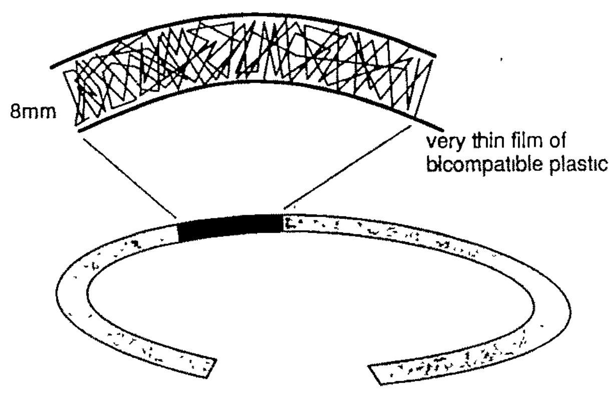

Figure 1 *Illustration of present design jacket*

kidneys can be stored for up to 72 h when cold, there are obvious advantages in preventing rewarming of the kidney before it is connected to the circulation of the recipient. Until now only basic attempts have been made to keep the kidney cool during the transplant operation, usually by wrapping it in gauze soaked with cold saline.

The aims of the study were to investigate the temperature changes that occur in the kidney during the vascular anastomosis phase of the transplant operation in an animal model, and to design a system that would keep the temperature of the cooled kidney below 10°C for 40 min. A realistic system would need to be simple to use, non-bulky, allow easy access to the renal vessels for anastomosis and be either disposable or easy to sterilize.

Materials and methods

An animal model was designed to reproduce the operative conditions that exist during the second warm ischaemic time of the transplant operation. Pig kidneys from the abattoir were used. The pigs were killed by stunning and exsanguination and their kidneys were removed within 20 min of death and cooled. Two methods of initial cooling were used. The kidneys were either infused via the renal artery with cold perfusate solution and then placed in ice, or placed in ice without prior infusion. The core temperature of the kidneys on removal from cold storage was the same regardless of which cooling method was used and comparisons were always made between paired kidneys which were cooled in the same way. All kidneys were placed in plastic bags and stored in crushed ice in the same way as human kidneys are preserved in the UK.

The two kidneys were removed from cold storage in an operating theatre. One kidney was wrapped in gauze soaked in ice-cold saline. The second kidney was placed in the system under test. If there was a size discrepancy between the two kidneys, the larger one was used as the 'test' kidney. Thereafter, the kidneys were subjected to exactly the same conditions. The energy striking the experimental surface was controlled as follows. First, the kidneys were supported on a thin film of plastic over a water bath, the temperature of which was maintained at 30°C. Secondly, energy from the operating theatre light was measured using a lux meter and maintained at 30 klx by adjusting the height and focus of the light. This figure represents a power dissipation of 142·5 mW/cm^2.

Temperature was measured using a minithermocouple probe attached to a digital meter data logger (Grant Instruments, Cambridge, UK). This enabled accurate temperature measurement to be made every minute for the first 5 min after removal from cold storage. Readings were then taken every 5 min up to 45 min. This time was chosen as it represents the upper limit of the second warm ischaemic time in clinical renal transplantation on our unit. Temperature measurements were recorded at four sites: (1) water bath, (2) air temperature at experimental surface, (3) core of kidney (control), and (4) core of kidney (test).

Cooling systems tested

Several systems were tested and discarded for a variety of reasons: continuous flow of cold saline or gas around the kidney (these methods were cumbersome and difficult to use); an envelope of ice around the kidney (this was bulky and difficult to handle); aluminium foil (this was much more pliable and moulded to the desired shape well, however, it did not perform well in laboratory bench tests because of accelerated heating in certain circumstances).

Consideration of the basic physics of the problem suggested that the thermal conductivity of the material in use was the major factor which could be altered without increasing the bulk of the 'jacket'. An easily available substance with a low thermal conductivity is air. It was from this simple idea that the prototype was developed and improved to become the system tested (*Figure 1*). It consists of two thin films of a biocompatible plastic, which sandwich a weave of a similar plastic containing air trapped among the fibres of the weave. The jacket thus formed measures 8–10 mm in thickness and can be used for small or large kidneys. It is closed around the hilum of the kidney by a simple draw cord which allows the renal vessels to protrude.

Results

Throughout all experiments, the water bath temperature was maintained in the range 27–33°C and the air temperature in the operative field was recorded as 28–38°C. Mean results over 12 paired experiments for these two parameters are listed in *Table 1*. On removal from the preservation system, the core temperature of all kidneys ($n = 24$) was 0–1°C (mean 0·6°C). In 12 paired experiments, the kidneys that were allowed to warm sustained a predictable rise in temperature of 2°C (mean 1·9°C) per 5 min interval, from 5–45 min. The core temperature of these kidneys was always above 10°C by 20 min. The final temperature at 45 min was 16–25°C (mean 19·6°C). The core temperature of the paired kidneys placed in a cooling jacket rose at a mean of 0·9°C per 5 min interval in the 5–45 min period. The mean temperature at 45 min was 8·0°C and was always below 10°C at this time. These figures are listed in *Table 1* and illustrated in *Figure 2*.

Table 1 *Mean temperatures recorded in 12 paired animal model experiments*

	Temperature (°C)			
Time (min)	Water	Air	Core kidney (normal)	Core kidney (test)
0	32·2	31·0	0·6	0·6
1	32·0	31·1	1·1	0·7
2	31·4	31·2	1·7	0·8
3	31·0	30·8	2·4	0·9
4	30·6	30·0	3·1	1·1
5	30·9	30·4	4·0	1·3
10	30·7	30·5	6·3	1·8
15	30·1	30·4	8·8	2·5
20	30·2	30·2	11·5	3·4
25	30·0	29·9	13·4	4·2
30	29·8	29·6	15·2	5·1
35	29·2	29·5	16·7	6·1
40	29·6	29·4	18·1	7·2
45	29·9	29·5	19·6	8·0

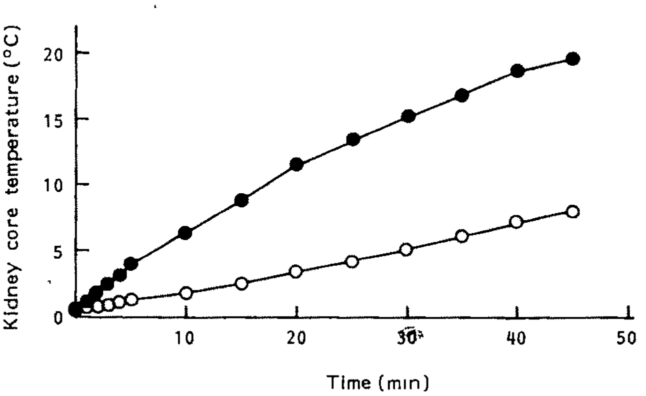

Figure 2 *Mean temperature recorded in 12 paired animal model experiments.* ●, *control kidney;* ○, *kidney with jacket*

Discussion

This study has demonstrated that the core temperature of kidneys stored before transplantation is between 0 and 1°C, a fact not always appreciated by transplant surgeons. It is important to place the kidney in fluid during ice preservation as failure to do so may allow freezing of the parenchymal tissue with resulting intracellular crystal formation and cell damage. Indeed, recent evidence suggests that such low temperatures may not be ideal for kidney preservation[11].

A number of studies have demonstrated that keeping a kidney cool during a period of ischaemia improves ultimate function[12,13]. It is the practice of some surgeons to pour aliquots of cold saline intermittently on to the kidney during the second warm ischaemic time. Nevertheless, in a separate experiment this was shown not to lower the core temperature and it had minimal effect on slowing the rate of temperature rise. To obtain a satisfactory cooling effect, cold saline had to be run over the kidney in a continuous stream.

Other methods of keeping the kidney cool[14] (using jackets) during the second warm ischaemic time have not met with acceptance owing to the bulk or complexity of such devices, which make the performance of the vascular anastomoses more difficult. The cooling system employed must not only keep the kidney cool but also must not handicap the surgeon. A jacket, such as the one described, is non-bulky, simple to use, disposable, and allows access to renal vasculature while still maintaining the kidney at a low temperature. This jacket is being commercially developed and when a suitable sterile form has been made it will be tested during clinical transplantation.

In the early days of transplantation it was recognized that ischaemic injury must be minimized. This objective has been largely achieved during the retrieval operation and during a limited preservation period. Slowing the rate of the temperature rise during the second warm ischaemic time will further reduce ischaemic injury and should, therefore, become part of clinical practice.

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Skin cancer in renal transplant recipients

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Skin cancer was found in 31 of 598 patients transplanted in Oxford. No cases occurred during the first 3 years after transplantation but the prevalence rose after 12 years to 18·2 per cent. The main risk factors predisposing to skin cancer were the time after transplantation and male sex. Comparison with data from other centres suggests that exposure to ultraviolet light is a major aetiological factor in the speed of development of skin cancer. As the incidence of new cases rose progressively with time in our patients, it would seem that skin cancer is likely to become a major clinical problem as more patients enjoy prolonged survival after renal transplantation. Preventative and screening measures should be taken by transplant units both in the UK and in other countries with similar temperate climates.

Keywords: Skin cancer, renal transplantation

Dermatological problems such as warts and solar keratosis occur frequently in renal transplant recipients with an incidence of up to 90 per cent in one large series[1]. Similarly, the incidence of cancer of all types is increased, being especially marked for lymphomas, cervical cancer and skin cancers[2,3]. However, the majority of these cancers appear on the skin and are predominantly squamous cell carcinomas[4,5].

The increased risk of development of skin cancer in renal transplant recipients has been described in populations with heavy sunlight exposure, such as those of Australia[5–7] and South Africa[8]. However, the incidence of skin malignancy in more temperate European climates is less well defined and has generally been thought to be less of a problem than in those closer to the equator. We have studied skin cancer in our centre to assess the incidence of this complication.

Patients and methods

From January 1975 to May 1988, 598 patients received 707 renal transplants in Oxford: 649 from cadaver donors and 58 from living related donors. In addition, 21 foreign patients received living related transplants, but they have been followed up abroad and are not included in this analysis. In the period of this study the form of immunosuppression has changed several times From 1975 to 1978 azathioprine and high dose steroids were used[9], and from 1978 azathioprine with low dose steroids were used[10]. In 1979 cyclosporin was introduced in trials with conventional therapy[11], followed by triple therapy with cyclosporin, azathioprine and steroids in 1985[12].

All transplant recipients are followed regularly in the outpatient department and the skin is systematically examined. All suspicious skin lesions are biopsied and, in addition, patients with known skin problems, either malignant or premalignant, are seen regularly by a dermatologist (V.A.V.) in a clinic devoted to dermatological surveillance in transplant recipients. A register of all histologically proved malignancies has been prospectively compiled In addition to squamous cell carcinoma, basal cell carcinoma and malignant melanoma, the register has included all patients with carcinoma *in situ* (Bowen's disease) and keratoacanthoma. The patients with keratoacanthoma were included as histological differentiation from squamous cell carcinoma may be difficult[13,14]. In our series all patients with this diagnosis also had a frank cutaneous malignancy. Dermatological conditions such as solar keratosis and viral warts are not considered in this study. Statistical analyses were performed using Student's t test, the χ^2 test and linear regression analysis as appropriate.

Results

Types, sites and number of tumours

Thirty-one of 598 patients (5 per cent) developed 98 skin cancers. Eight (26 per cent) of these patients had single lesions, eight (26 per cent) had multiple lesions of the same histological type and 15 (48 per cent) had multiple lesions of more than one histological type (*Tables 1* and *2*). *Figure 1* shows the anatomical distribution of these cancers, which were most commonly found on sun exposed areas of the body. *Figure 2* shows the prevalence of affected patients in the transplant population and *Figure 3* shows the incidence of new cases per year in previously unaffected patients. The data in *Figures 2* and *3* are for patients with functioning first grafts only.

Table 1 *Histological types of skin cancer in 16 patients with lesions of one histological type only*

Type of cancer	Total number of patients affected	Number of patients with single lesions	Number of patients with multiple lesions (number per patient)	Total number of lesions
Bowen's disease (carcinoma *in situ*)	1	1	0	1
Squamous cell cancer	11	6	5 (2, 2, 2, 5, 7)	24
Basal cell cancer	3	2	1 (2)	4
Malignant melanoma	1	1	0	1
Total	16	10	6	30

Table 2 *Combinations of skin cancer in the 15 patients with multiple malignancies of different histological types*

Type of skin cancer	Number of patients (number of lesions per patient)	Total number of lesions
Bowen's + SCC	3 (2, 2, 3)	7
SCC + BCC	1 (3)	3
SCC + KA	3 (3, 5, 9)	17
SCC + KA + BCC	1 (5)	5
BCC + SCC + Bowen's	1 (3)	3
Bowen's + SCC + KA	3 (3, 4, 11)	18
Bowen's + BCC + KA	1 (5)	5
Bowen's + SCC + KA + BCC	2 (5, 5)	10
Total	15	68

SCC, squamous cell cancer, BCC, basal cell cancer; KA, keratoacanthoma

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R. M Higgins is a Wellcome Training Fellow.

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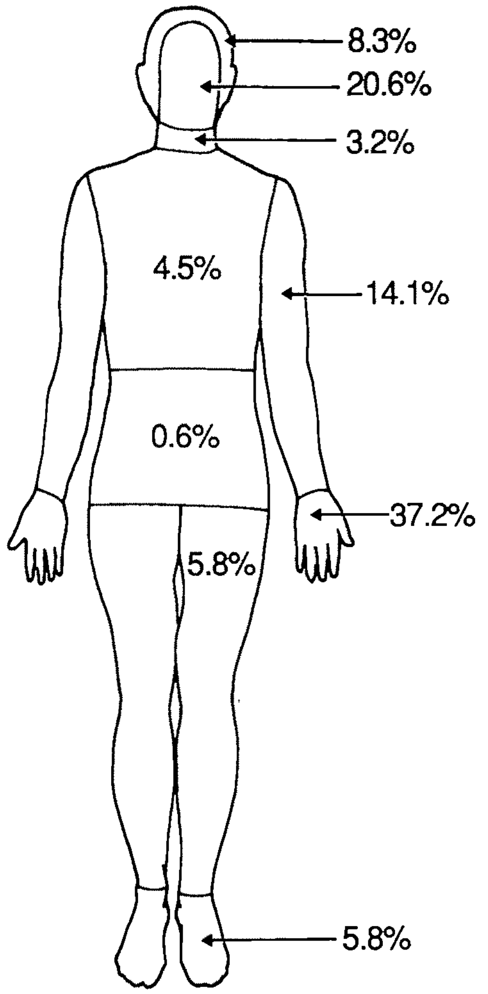

Figure 1 *Distribution in the body of 98 skin cancers*

Age and sex

The mean age at the time of transplantation of the patients who subsequently developed skin cancers was 41·9 years (range 11–67 years). This was not statistically different from the mean age at the time of transplantation of all other recipients (mean age 39·2 years, range 7–67 years). Skin cancers developed in five (2·3 per cent) of the 222 female renal transplant recipients and in 26 (7·9 per cent) of the 370 male recipients. The higher incidence in male recipients is statistically significant ($P < 0{\cdot}05$).

Type of underlying renal disease

There was no difference in the incidence of the various conditions causing end-stage renal failure in the patients with or without skin cancer.

Type of immunosuppression

The incidence of skin cancer was not related to the type of maintenance immunosuppression used. Three patients with skin cancer received cyclosporin together with prednisolone and/or azathioprine, and 28 received azathioprine and steroids. There was no statistical difference in the incidence of skin cancer in patients given azathioprine with high or low dose steroids. No patient given antithymocyte globulin has subsequently developed a skin cancer although the follow-up is less than 3 years .

Time to detection of cancer

The mean time from transplantation to diagnosis of the first skin cancer was 84·6 months (range 43–132 months). In the 18 patients who developed a second cancer, the mean(s.d.) interval between detection of the first and second cancers was 15(12) months. In the 11 patients who developed a third cancer, the mean(s.d.) detection interval between the second and third cancer was 11(9) months. This tendency toward a shorter detection interval with subsequent cancers was not statistically significant but the numbers in our series are small. *Figure 4* shows data from five patients, all with four or more malignancies. If it is assumed that after the second new cancer these tumours developed at a constant rate, linear regression analysis demonstrates a mean(s.d.) growth/detection rate of 0·11(0·11) cancers per month, which represents a mean rate of development of 8·9 months per cancer in these patients.

Treatment and outcome

All patients were treated by excision of the tumour and other suspicious areas. One patient was also treated with local radiotherapy after excision of a squamous cell cancer. The single patient with malignant melanoma had wide local excision and a split skin graft. There have been no regional or distant metastases to date from any of the skin tumours. One patient who developed axillary lymphadenopathy following excision of a forearm squamous cell carcinoma was subjected to axillary lymph node dissection, but histological examination showed no evidence of tumour. In one patient, widespread perianal squamous dysplasia and carcinoma *in situ* were treated by wide excision and withdrawal of immunosuppression. His graft failed, and he remains well on maintenance haemodialysis, although there are still some residual skin changes which are felt to preclude retransplantation with the need for reinstitution

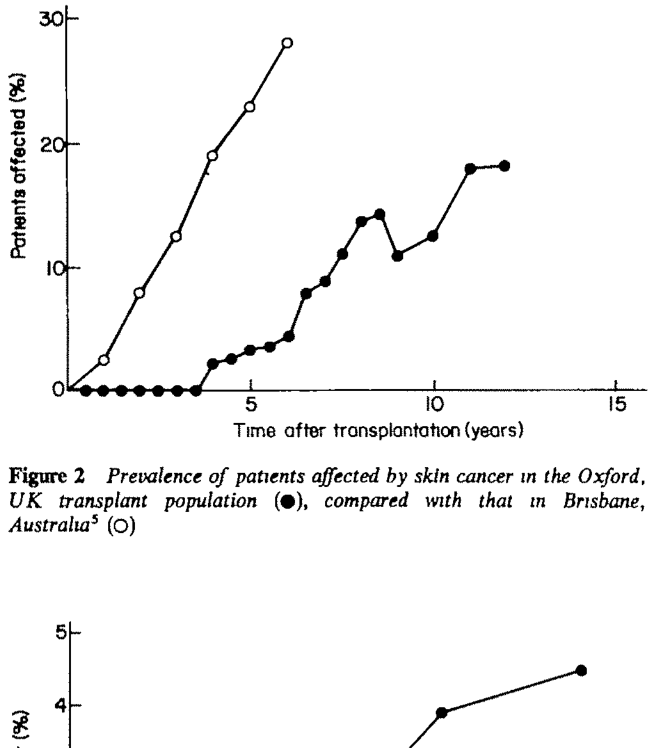

Figure 2 *Prevalence of patients affected by skin cancer in the Oxford, UK transplant population* (●), *compared with that in Brisbane, Australia*[5] (○)

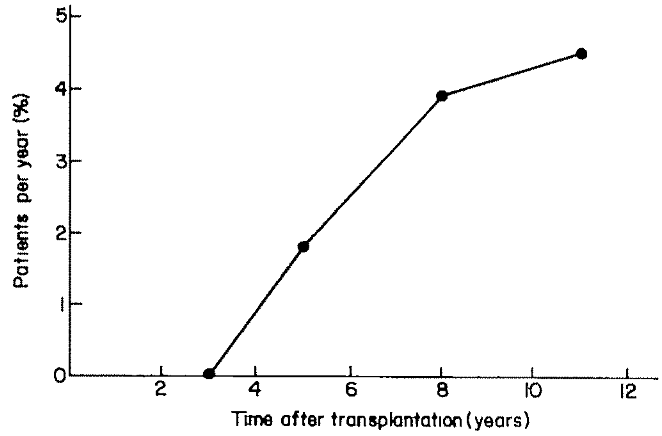

Figure 3 *Incidence of new cases of skin cancer in previously unaffected transplant patients*

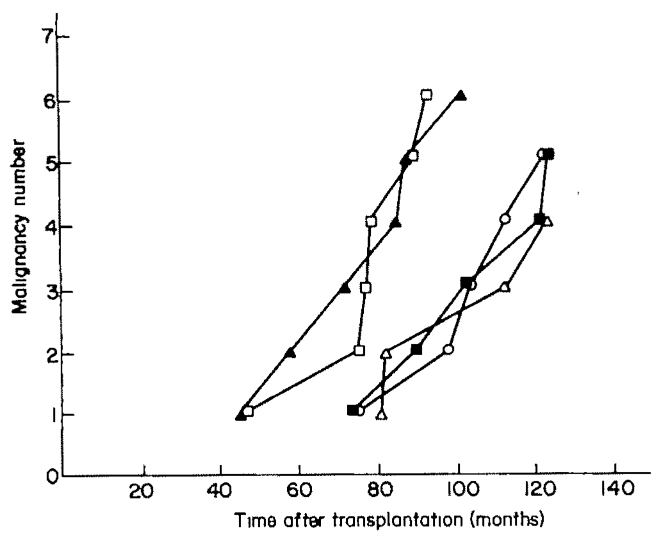

Figure 4 *The occurrence of skin cancers with time in five patients who have experienced multiple cancers Linear regression analysis shows a mean interval of 8 9 months between the occurrence of each new cancer*

of immunosuppression. One patient who experienced multiple squamous cell carcinomas of the skin developed a poorly differentiated non-Hodgkin's lymphoma and has died from this. Another patient has died from an unrelated condition.

Discussion

The aetiology of skin cancers in renal transplant recipients is multifactorial and includes exposure to ultraviolet light, immunosuppressive drug treatment and viral infection. Genetically determined skin type and colour are also important, but the discussion will be confined to Caucasian patients, as they form the principal risk group.

The most important risk factor predisposing to skin cancer was time from transplantation and hence the duration of immunosuppressive therapy, and this was irrespective of the age of the patient at transplantation. Thus, cancer should be suspected in all transplant patients with suspicious skin lesions whatever their age, although in our patients we did not see any cancers until more than 3 years after they had first received a renal transplant.

The relative risk of developing a skin cancer in patients with a renal transplant compared with the general population increased with time after transplantation to about 100-fold. The incidence of squamous cell cancer in the general population in the UK has been calculated at 7·5 cases per 100 000 per year[15]. The incidence of new cases of skin cancers in previously unaffected transplant patients rose to over 3500 per 100 000 population in year 8 after transplantation, with a trend to a further increase with time (*Figure 3*). By comparison, the state of Queensland in Australia has the highest incidence of skin cancer in the world, with 211 cases per 100 000 of the general population per year, and the relative risk of developing skin cancer during year 9 after transplantation is also about 100 times that of the general population[5] As these calculations do not take age-related risk into consideration, the true relative risk may be underestimated.

Ultraviolet light causes many of the changes that lead to skin cancer. As has been noted in previous reports on renal transplantation, the majority of malignancies in our patients developed in areas of the body exposed to the sun (*Figure 1*). However, we were unable to relate the incidence of cancer in our patients to outdoor occupations, in contrast to another study from the UK where such a relationship was established after prospectively interviewing the patients[16]

Exposure to ultraviolet light is also related to the geographical latitude of individual transplant centres. It is difficult to compare the incidence and prevalence of skin cancer in different centres around the world. Most reports do not show the prevalence related to time after transplantation, and do not report the incidence of new cases in their patients as we have done in this analysis Comparable data are available from Brisbane, Australia[5], and their results are compared with ours in *Figure 2*. The prevalence of skin cancer is not only higher in Brisbane than in Oxford, but the cancers appear sooner after transplantation. The prevalence of skin cancer in other UK centres is probably similar to that in Oxford[16–18]. In Götenburg, Sweden, there is a striking similarity to our results, with no cases in the first 3 years after transplantation, and a rise in prevalence to about 20 per cent by 12 years after transplantation[19].

Although there are little data on the prevalence of skin cancer with time after transplantation, several centres report the mean time from transplantation to detection[5,14,20]. These data are biased to only a minor extent by variations in duration of follow-up in different centres. The speed of development of skin cancer is related to the latitude of each transplant centre, again confirming the importance of exposure to ultraviolet light (*Table 3*).

The details of the mechanisms whereby ultraviolet light leads to skin cancer are unclear. The DNA of keratinocytes may be damaged by sunlight[21] and such potentially oncogenic changes may be potentiated by photo-oxidative effects of the metabolites of azathioprine[22,23]. It has recently been shown that, in an *in vitro* model, glucocorticoids together with human papilloma virus and the human *ras* oncogene may lead to the oncogenic transformation of otherwise normal cells[24]. Viral infection may play an important part in the development of these cancers and human papilloma virus has been identified in a number of cases of squamous cell carcinoma[25–28]. A causative role for this virus in the development of skin cancer in transplant patients is one possible explanation for the observation that the incidence of squamous cell cancer is higher than that of basal cell cancer, in this series as in previous reports[2,6,7]. This is in contrast to the general population, where basal cell cancer is more common than squamous cell cancer.

Although treatment with immunosuppressive drugs does predispose to skin cancer[3,6], there is no evidence from clinical trials to suggest that any particular immunosuppressive drug is a dominant risk factor. Cyclosporin has not been in use long enough to draw any firm conclusions about whether it confers a greater or lesser risk than other drugs. However, there has been concern about the future possible development of skin cancer with cyclosporin due to the development of photosensitization in sunlight and a generalized increase in squamous epithelial growth[29]. In this series, the follow-up time is too short to assess the relative risk of cyclosporin treatment. However, one study has shown no difference between the incidence of skin cancers in patients randomized to receive either cyclosporin or prednisolone and azathioprine during a 5-year follow-up period, but the number of affected patients in the study was very small[30].

Male patients receiving transplants were more likely to develop skin cancer after transplantation than female patients in this study, as also noted previously[6,8]. The reason for this is unclear, although differences in sun exposure, hormonal

Table 3 *Mean time from transplantation to detection of cancer related to the geographical latitude of various transplant centres*

Transplant centre	Latitude (degrees)	Mean time from transplant to detection of skin cancer (months)
Oxford	52	84 6
Wisconsin[14]	45	78
Denver, Colorado[20]	40	58
Brisbane, Australia[5]	34	32 6

responses or skin types might all be relevant. In one report it has been suggested that the development of some skin cancers may be related to recipient human leucocyte antigen (HLA) type. Basal cell carcinoma was associated with a higher than expected frequency of HLA-A1 and lower than expected frequency of HLA-B12 (K.I. Welsh, E. Higgins, A.M. Tidmos *et al.*, unpublished results). However, in our patients there was no such relationship.

Other series have noted that skin cancers in transplant patients may be unusually aggressive, with deaths and nodal metastases[2,6,7]. These aggressive cancers have been recorded in Australia and New Zealand and it may be that the skin cancers in temperate Europe are less of a threat.

Prevention of skin cancers is an important feature in routine follow-up in many transplant centres, although it is unclear how much difference active preventative measures actually make. We advise our patients to keep out of the sun as far as possible and to wear long sleeved shirts and brimmed hats when in the sun. Skin creams that provide total block to ultraviolet light are also recommended. Early detection of cancer makes surgical excision easier and reduces the risk of tumour spread, so that our patients are advised to check their own skin in addition to the routine checks at outpatient follow-up visits. The use of systemic retinoids appears to be very effective in patients with solar keratoses and warts, but may be less effective in those with multiple squamous cell cancers[31]. Further studies of the efficacy and safety of retinoids are indicated, but they may become important therapeutic and preventative agents in some patients.

In conclusion, although skin cancer in renal transplant recipients in the UK is less aggressive and occurs later after transplantation than in countries closer to the equator, it is still a significant cause of morbidity. As the risk of developing skin cancer seems to be primarily related to the duration of immunosuppression, it is likely to become a more significant problem in the future as more patients survive for longer periods with a functioning graft.

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Analysis of 828 servicemen killed or injured by explosion in Northern Ireland 1970–84: the Hostile Action Casualty System

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Death and injury due to terrorist bombings continue to exercise civilian and military surgeons alike. In this paper 828 servicemen killed and injured by explosions in Northern Ireland have been studied, using data stored in the Hostile Action Casualty System (HACS). Because of the nature of the conflict in Northern Ireland, the magnitude of each explosion and the distance of the victims from it are quite accurately known. The overpressure (blast loading) to which the victim was exposed can be estimated from the information on the HACS forms and standard tables, giving overpressures for a given charge at a known distance. Using the HACS data, the numbers of injuries due to overpressure (primary blast injury), missiles energized by the blast (secondary injury), displacement of the victim by the blast wind (tertiary injury) and flash burn can be determined. Of the 828 servicemen involved in explosions, 216 were killed, most of them before any treatment could be instituted. Of the servicemen in the survey, 90 per cent were wearing body armour. Although body armour affords considerable protection from secondary missiles, it is unlikely to reduce the number of deaths due to primary blast injury.

Keywords: Explosions, blast injury, Hostile Action Casualty System

Terrorist bombings are a major cause of death and severe injury in both civilian and military practice. The patterns of injury caused by blast are complex. In this paper, the injuries caused by explosions in 828 servicemen serving in Northern Ireland between October 1970 and May 1984 have been studied, using data stored in the Hostile Action Casualty System (HACS)[1]. Because of the nature of the troubles in Northern Ireland, the magnitude of each explosion and the distance of the victims from it are quite accurately known. Using this information the approximate overpressure to which the victim was exposed can be estimated, and so the number and type of injuries related to the severity of the blast loading can be determined: namely, blast lung injury, displacement of the victim by the blast wind, flash burn injuries and impact of missiles energized by the blast. The significance of these findings in the light of recent research into the nature of blast injury is discussed.

Methods

The HACS was set up by Lt Col. Owen-Smith in the late 1970s, while he was Professor of Military Surgery, to fulfil a need for accurate analysis of wounds sustained in action, their treatment and the end result[1]. Because of the nature of the troubles in Northern Ireland it is possible to obtain forensic data on each incident. Thus the magnitude of an individual explosion in each incident can be ascertained. A standard form (the HACS coding sheet) is completed for each injured serviceman. The relevant information for size of explosive device and distance from the casualty is shown in *Table 1*. The various combinations of weight of explosive and distance are given as a serial number for computer coding.

The stored information pertaining to those servicemen killed or injured by explosions between October 1970 and May 1984 was studied with particular reference to the size of the charge and the distance of the victim from it.

Using standard data (examples of which are given in *Figure 1*), each of serials 30–44 (*Table 1*) could be allocated to one of four groups denoting the severity of blast loading (*Table 2*). During the period under review, commercial rather than military explosive was used and the grouping is based on the blast produced by commercial blasting gelignite with a detonation velocity of about 4000 m/s (rather less than that of trinitrotoluene). Those in group 1 would have been exposed to the lowest overpressure (predicted to be only sufficient to cause ruptured tympanic membranes), whilst those in group 4 would have been exposed to the highest overpressure (predicted to be sufficient in a high proportion to cause severe, probably fatal primary lung injury).

Results

Between October 1970 and May 1984, explosions accounted for the deaths of 216 servicemen, 31 of whom were totally disrupted. The survivors were classified as having had major, moderate or minor injuries. There were 92 major, 89 moderate and 431 minor injuries. *Table 3* shows the distribution of degree of injury within the four groups described in *Table 2*. The majority (90 per cent) of the servicemen killed or injured by explosions in this period were wearing body armour. Less than 20 per cent wore helmets.

Table 1 *Extract from Hostile Action Casualty System (HACS) form*

	Distance (ft)†		
Size (lb)*	<10	10–50	>50
2	30	31	32
2–6	33	34	35
7–20	36	37	38
21–99	39	40	41
>100	42	43	44

Serial numbers 30–44, bomb blast by size and distance. group 1, minor blast loading: serial numbers 31, 32, 34, 35, 38, 41, 44; group 2, moderate blast loading: serial number 37; group 3, severe blast loading. serial numbers 30, 40, 43; group 4, very severe blast loading: serial numbers 33, 36, 39, 42. * 1 lb≈0 45 kg, † 1 ft≈0 3 m

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Modes of death

Table 4 shows modes of death related to the estimated blast injury sustained. Apart from those who were totally disrupted by the blast, the remainder fell into four distinct subgroups. The first and largest subgroup of fatalities had mixed patterns of injuries including head, chest and secondary missile injuries. The significance of each component in any fatality is uncertain, although in group 4 'blast lung' (see below) was present in all cases in which forensic reports were available.

In groups 1, 2 and 3 there was a second subgroup in which head injury alone was an important cause of death. There is a third subgroup of fatalities in group 4 with head and chest injury (in the form of blast lung) alone. The fourth distinct subgroup, 'severe chest injury alone', is that in group 4. Servicemen in this subgroup died with no serious external injury. Their mode of death is discussed below.

Of the 216 fatalities, 174 were dead before any assistance could be rendered. Twelve died in hospital, of overwhelming injuries, whilst resuscitation was being commenced, and seven died on the operating table. Twenty-three patients died after initial resuscitation: of these, seven died peroperatively (three of severe head injuries with massive intracerebral haemorrhage, one of uncontrollable intra-abdominal and intrathoracic bleeding, two of blast lung in the form of massive haemoptysis, and one of the effects of a major traumatic amputation).

Sixteen survived their initial operations. Eight died of severe head injuries, four of whom had no other injuries. Seven survived their operations but died of blast lung, although whether this could be ascribed solely to blast-induced pulmonary contusion or was aggravated or indeed caused by sepsis or prolonged hypovolaemic shock is by no means clear. These factors probably contributed to the death of the patient with the traumatic amputation (*Table 5*).

Survivors requiring laparotomy and/or ventilation

There were only five patients who fell into this category and all had been in vehicles involved in accidents as a result of an explosion. One was in group 2 and required suture of stomach and liver alone. Two were in group 4; both required ventilation following laparotomy, and one required elevation of a skull fracture. Two survivors from group 3 (severe blast loading) with no external injuries had lung damage severe enough to warrant ventilation.

Incidence of perforated eardrum in survivors of blast

There were 288 survivors of explosions who had perforated eardrums. This occurred in about 50 per cent of the survivors

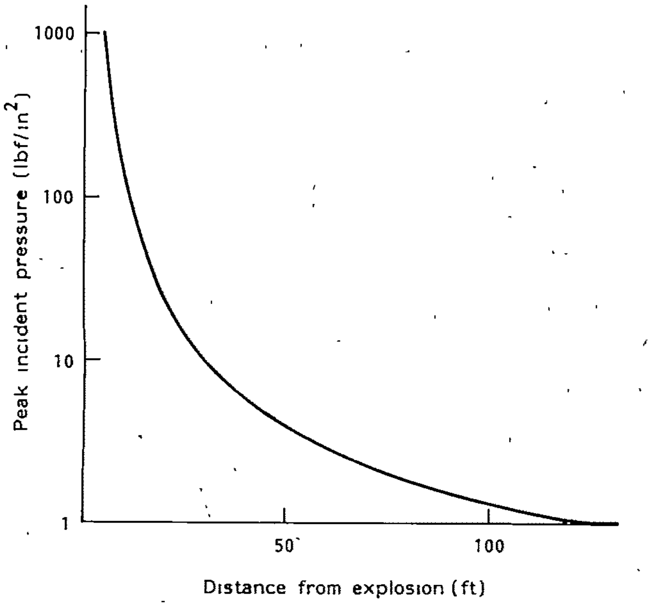

Figure 1 *Standard curve showing the decay in incident pressure of the blast wave against distance for a 50 lb charge of trinitrotoluene. The overpressure is inversely proportional to the cube of the distance from the explosion for a given charge. (Non-SI units are used to correspond to the Hostile Action Casualty System (1 lbf/in^2 ≈ 6·9 kPa) forms.)*

Table 2 *Victim groups according to blast loading*

Group	Overpressure (lbf/in^2)*	Blast loading
1	<20	Minor: maximum overpressure sustained sufficient to cause ruptured tympanic membrane
2	20–50	Moderate higher overpressure than group 1, but probably insufficient to cause primary lung damage in a significant number of casualties
3	50–80	Severe: sufficient overpressure to cause primary lung damage in a significant proportion of casualties
4	>80	Very severe: sufficient overpressure to cause severe primary lung damage with a significant incidence of death

* 1 lbf/in^2 ≈ 6·9 kPa

Table 3 *Degree of injury related to estimated blast loading in 828 servicemen*

	Group			
	1	2	3	4
Number of cases	255	135	200	238
Disrupted	0	4 (3·0)	4 (2)	23 (9·7)
Dead	5 (2·0)	24 (17·8)	34 (17)	122 (51·3)
Major injury	14 (5·5)	13 (9·6)	38 (19)	27 (11·3)
Moderate injury	23 (9·0)	16 (11·9)	35 (17·5)	15 (6·3)
Minor injury	213 (83·5)	78 (57·8)	89 (44·5)	51 (21·4)

Values in parentheses are percentages

Table 4 *Cause of death related to estimated blast sustained in 216 servicemen*

	Group			
Cause of death	1	2	3	4
Number of cases	5 (2·3)*	28 (13·0)*	38 (17·6)*	145 (67·1)*
Total body disruption	0	4 (14)	4 (10)	23 (16)
Head injury alone	2 (40)	8 (29)	6 (16)	10 (7)
Severe chest injury alone	0	0	0	24 (17)
Head and chest injury	0	6 (21)	10 (26)	30 (21)
Secondary missile injury with head and/or chest injury	0	10 (36)	18 (47)	58 (40)
Other	3 (60)	0	0	0

Values in parentheses are percentages of the number of cases in the group or * of the total number of cases

Table 5 *Postoperative deaths following blast injury*

Group	Injuries	Operation	Cause of death
1	Multiple secondary missile wounds	Wound toilet	ARDS
	Head, chest, abdomen	Splenectomy, nephrectomy	Head injury
2	Head, chest, abdomen	Thoracotomy, splenectomy, liver suture	Head injury
	Chest, abdomen	Cardiac suture, splenectomy, liver suture	ARDS
	Head, chest, abdomen	Laparotomy	Head injury
3	Traumatic amputation	Wound toilet	?
	Head, chest, traumatic amputation	Wound toilet	Head injury
	Head, chest, abdomen	Cardiac suture, splenectomy	ARDS
4	Traumatic amputation, chest, abdomen	Wound toilet, liver suture	ARDS
	Chest, abdomen	Splenectomy	ARDS
	Traumatic amputation, chest, abdomen	Wound toilet, liver suture	ARDS
	Traumatic amputation, chest, abdomen	Wound toilet, liver suture	ARDS

Where ARDS (adult respiratory distress syndrome) has been cited as a cause of death, it cannot be stated whether this was due to the primary effects of the blast itself or other causes such as shock, sepsis, etc. A further four died solely of head injury

Table 6 *Numbers of blast victims and percentage with ruptured tympanic membranes related to estimated blast loading*

	Group			
	1	2	3	4
Fatalities ($n=216$)	5 (0)	28 (60)	38 (78)	145 (96)
Survivors ($n=612$)	250 (47)	107 (52)	162 (49)	93 (38)
All blast victims ($n=828$)	255 (48)	135 (60)	200 (55)	238 (83)

Values in parentheses are percentages

in each of groups 1–3 (*Table 6*). The percentage of survivors in group 4 with perforated eardrums was rather lower, although when those who died of blast injury are included (all of whom had perforated eardrums) there is a much higher incidence in group 4. None of the five who survived laparotomy and/or ventilation had perforated eardrums. In all, 137 sustained permanent hearing loss.

Head injuries

One hundred and fifty two servicemen who died from blast injury had head injury as a contributory factor. Of these, 25 were killed by head injury alone, 44 by a combination of head injury and blast lung alone, 24 by head injury, blast lung and intra-abdominal injury, and 56 had additional secondary missile injuries. Five patients with severe head injury alone survived long enough to be ventilated, but only one of these recovered

Of 113 with less severe head injuries, seven were left with some form of central nervous system defect attributable to the injury.

Limb injuries

In all, 298 servicemen sustained limb injuries, 106 of whom sustained lower limb injuries, 89 upper limb injuries, and in 103 both the upper and lower limbs were injured. Of these, 45 had residual lower limb problems, sufficient to require late amputation in two instances, 21 had residual upper limb problems, and two had late amputation.

The majority of these injuries were caused by secondary missiles. When traumatic amputation caused by the blast wind occurred, survival was limited (*Table 7*).

Burns

Only 31 servicemen sustained burns as part of their injury. Of these, three in group 4 died (of other injuries). In the remainder, burns were superficial and healed without complication.

Table 7 *Traumatic amputation following explosion in 52 servicemen*

	Group			
	1	2	3	4
Died	0	2	9	32
Survived	0	1	5	3

Discussion

An explosion is essentially a rapidly expanding sphere of high-pressure, high-temperature gaseous products, resulting from the rapid chemical decomposition of the explosive substance. The sphere is known as the blast wave and reaches its maximum overpressure virtually instantaneously. The wavefront reduces in pressure as an inverse cube of the distance from the explosion (*Figure 1*). The wavefront propagates through the air, and mass movement of air displaced by the explosive products causes the blast wind that follows an explosion, which is known as the dynamic pressure. When the blast wave interacts with an object in its path important phenomena occur. Part of the incident wave is reflected and reinforces the oncoming wavefront and may increase the local overpressure up to eightfold. A stress (pressure) wave may couple into the object. If it reaches an interface between areas of differing densities, part is reflected and part continues on. Pressure differentials (stresses) occur at the interface between media of differing density. These stresses are most marked at air–fluid interfaces, so that in the body the lung is most readily affected. The pressure differentials across alveolar–capillary interfaces may disrupt the barrier, resulting in haemorrhagic contamination of alveoli (blast lung).

Secondary injuries are caused by fragments of casing, glass and masonry energized by the explosion. The blast wind accelerates bodies in its path, causing injuries of varying severity, including traumatic amputation (so-called tertiary injury). Flash burns and local fires will occur due to the intense local heat of the explosion, although this soon dissipates with time and distance from the explosion. In this survey, most of the burns were of the 'flash' type, as the amounts of explosive used in terrorist bombs during this period were for the most part relatively small (see below). Clothing generally provides adequate protection from flash, and burns tended to be superficial and healed without complication.

From the clinical point of view, the important effects of the blast wave itself, in the absence of significant penetrating wounds, are ruptured tympanic membrane, primary lung damage, traumatic amputation and death. The four groups described are broadly based on the minimum overpressure required to produce these phenomena (*Table 2*). It has been stated that exposure to significant blast is unlikely if the victim has intact ear drums[2], and only 38 per cent of survivors in group 4 were recorded as having ruptured ear drums (*Table 6*). There are three possible explanations.

Firstly, although the threshold for rupture of the exposed tympanic membrane may be as little as 2 kPa, the loading on the tympanic membrane depends critically on the orientation of the head towards the incident wave. Secondly, although the victims in this group were close to a blast of some magnitude, there are many factors, such as position of furniture, pillars, cars and other victims, that could reduce the blast loading on the body within confined spaces[3]. However, loadings may increase owing to reinforcement of reflected waves. This accounts for severe blast injury in victims at what would normally be a safe distance from the explosion. Thirdly, the presence of ruptured tympanic membrane is probably under-reported, particularly in the severely injured where it may escape attention. In the forensic reports obtained, ruptured tympanic membrane had been reported in all those exposed to severe blast.

It has been generally accepted for many years that pulmonary contusion occurs as a result of compression of the lungs between rib cage and thoracic spine. Gross deformation of the rib cage can certainly be seen on high-speed cinephotography, but may not be primarily responsible for the lung injury. Cooper and Taylor[4] have identified three other mechanisms by which blast may cause internal injury. These involve the propagation of waves through the body in the form of stress waves, shock waves and shear waves.

Stress waves are longitudinal pressure waves similar to sound waves. They travel through tissue at roughly the same speed as sound waves but have a much higher amplitude. Shock waves are a special form of stress wave having a very high pressure and causing effectively an instantaneous wavefront propagated at a velocity much faster than that of sound through tissue. Shear waves are transverse waves of long duration and very low velocity, which produce gross distortions of tissues and organs.

Recent experimental studies[4] suggest that propagation of the stress waves described above may be the principal factor producing lung injury. Reinforcement and reflection of the pressure wave off the mediastinum causes a complex pressure environment within the lung parenchyma[5]. This is most pronounced at the alveolar–capillary membrane and results in pressure differentials across the barrier which allow leakage of blood into the alveolar spaces along with interstitial fluid. The low-velocity waves described above may cause shearing of lung tissue off the larger, more rigid bronchioles, causing further haemorrhage into the lung. Thus, the worst damaged areas generally appear where the stresses are greatest, in hilar and peripheral regions of the lung parenchyma.

Experiments done on animals during the Second World War showed that those within 18–30 ft of a 70 (31·5 kg) lb charge died of 'bilateral traumatic haemorrhage into both lungs. None survived at this distance, although others further away were not harmed in any way'[6]. This illustrates how rapidly the force of the blast wave drops away with distance.

With lesser degrees of blast, limited areas of blast contusion are seen. These may be related to the larger bronchioles or specific lobules. They do not seem to be very important clinically. Only two servicemen out of 828 suffered a degree of blast lung, with no external injury, which did not kill them but required ventilation for a period. It is likely that more severe but non-fatal degrees of blast lung occurred but were associated with other fatal injuries, or multiple injuries fatal in combination. Thus, looking at group 4 (*Table 4*), the majority died of multiple injuries as well as blast lung, although there were ten who appear to have died of their head injury alone.

Of deaths in group 4, 17 per cent occurred with no external injury. The majority of these probably died of blast lung, but a small percentage had inconclusive findings at post mortem. Air embolism has been cited as the cause of sudden death in these cases[3,7], and has certainly been demonstrated experimentally. Air embolism is also said to occur if blast victims are mechanically ventilated. There is no objective or experimental evidence for this and the phenomenon has not been commented on in any forensic report examined in this survey. This does not mean it does not occur, as air embolism is extremely difficult to detect unless specifically sought. It may be that in non-fatal degrees of blast lung there is insufficient damage for this to occur to any significant degree. The two servicemen who required mechanical ventilation for blast lung do not seem to have had any untoward effects in this regard. Cardiac dysrhythmias may occur as the blast wave passes, without any macroscopic or microscopic effect on the heart.

The number of deaths without external injury is higher than suggested by Cooper *et al.*[3], who were dealing with a civilian population. They maintain that sufficient proximity to the explosion to cause blast lung would entail equally fatal secondary missile injuries. This was the case in about one-third of the fatalities in this survey, but it is important to note that most of the injured wore body armour. Undoubtedly the body armour worn by most servicemen on patrol in the city would protect against penetrating chest injuries in the high blast group but not against the blast wave itself. There is some evidence to suggest that armour made of Kevlar® (Du Pont) may enhance the blast wave, although this effect is insignificant compared with the protection afforded against secondary missiles of both low and high velocity[8]. Both the survivors who required mechanical ventilation for blast lung had worn body armour and consequently had little in the way of external injury.

Head injury was the second most important cause of death and was a factor in 126 deaths and the sole injury in 26. It is tempting to surmise that deaths were caused by haemorrhage into the brain by shearing of vessels as the blast wave passed or motion of the brain within the skull. This may be true in the higher blast groups. However, most had evidence of external injury to the head so it is far more likely that the head was injured by flying debris, or by striking something when the victim was thrown by the explosion, particularly where head injury was the sole cause of death. Helmets were worn by less than 20 per cent of servicemen injured in this survey. Wearing helmets could have prevented deaths but at the expense of some mobility in the urban warfare environment.

Severe intra-abdominal injuries do not occur as an isolated phenomenon following exposure to blast, as the lung parenchyma is much more readily affected.

Looking at postoperative deaths following blast injury (*Table 5*), it is clear that chest and head injury decide survival. Blast injury severe enough to cause gut, liver or spleen injury usually causes fatal lung damage in air This is the case in the postoperative deaths in group 4, although those in groups 1 and 2, and to some extent group 3, died of their head injury. A notable exception is the first group 1 victim, who died of lung problems despite a relatively small explosion It may be that he developed adult respiratory distress syndrome (ARDS) as a result of his injuries rather than the blast itself. Where lung problems appear some time after the initial injury, it may be that some cause of ARDS other than blast should be invoked The post-mortem appearances will be much the same whatever the cause of ARDS.

There were only three survivors of laparotomy after an explosion, and they were all injured while in cars. This suggests that the injuries were due to compressive forces alone when the car was thrown by the explosion, and that the occupants were given some protection from the blast wave by the car body.

Those close enough to an explosion to suffer traumatic amputation are unlikely to survive the effect of the blast wave. Only nine of 52 suffering traumatic amputation survived. The remainder succumbed to chest or head injury.

In summary, a quarter of the 828 soldiers injured by explosions in Northern Ireland died. Chest injury was noted in three-quarters of the fatalities and, apart from a small group in whom no cause of death could be detected, the remainder died of head injuries. Sixteen patients died after surgery, of whom seven died of progressing ARDS. Whether the lung damage was primarily due to blast in these cases cannot be stated definitely. None of these deaths appears to have been avoidable. Only three patients survived laparotomy following explosions, and they were protected from the worst effects of the blast wave by being in cars.

By contrast, virtually all the injuries seen in survivors were caused by secondary missiles, rather than the blast wave itself. However, two blast victims without external injury survived lung damage severe enough to warrant mechanical ventilation. Such patients must be recognized and treated appropriately.

Body armour offers considerable protection against penetrating injury but is unlikely to protect against the effects of the blast wave. As a result, survivors of explosions wearing body armour may be seen with little in the way of external injury to the chest, but with more or less severe degrees of blast lung.

Research into the influence of armour on the pulmonary consequences of blast loading to the body and the most appropriate means of protecting the chest is continuing, with the aim of improving the chances of survival of servicemen exposed to terrorist bombings.

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Clinical decision making and laparoscopy versus computer prediction in the management of the acute abdomen

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A prospective study has been undertaken of 321 patients with acute abdominal pain admitted to hospital under one surgical firm over a period of 21 months. During the first 10 months patients were classified on admission according to the perceived need for operation, with laparoscopy being performed on all those in whom the need for operation was uncertain. In addition, all women with suspected appendicitis underwent laparoscopy because previous studies by us and others have demonstrated a high error rate in this group. During the second 11 months of the study a similar system of classification and procedure was used but the patient's initial assessment was entered on a structured data sheet. After the patient had been discharged home this information was entered into a computer-aided diagnosis program. Hypothetical retrospective computer-aided decisions were then made about patient management. The final management error rate (correct decision to operate or not) was compared with the actual error rate using the clinical system. The final overall error rate in the first 10 months was 11 out of 163 patients and this was improved to 3 out of 158 in the second 11 months of the study by the addition of the structured data sheet to selective laparoscopy. A management policy based entirely on diagnostic probabilities taken from the computer-aided diagnosis program would have produced an error rate of 26 out of 158. We conclude that in the management of the acute abdomen a policy based on clinical decision combined with selective laparoscopy may be superior to one based on diagnostic probabilities alone. Further improvement in results follows the introduction of a structured data sheet for initial data collection.

Keywords: Acute abdomen, laparoscopy, computer, diagnosis

In the handling of the acute abdomen performance must be judged ultimately against the number of correct or incorrect clinical decisions – the management error rate. We have recently demonstrated the value of selective laparoscopy in the management of patients with acute abdominal pain[1] where the procedure is used in those patients in whom the clinical decision to operate is indeterminate. Further analysis of the results from this study demonstrated that without laparoscopy the incidence of removing normal appendices in women was twice that in men[2]. We therefore changed our practice so that all women with suspected appendicitis would undergo laparoscopy before appendicectomy, a policy with which many others agree[3–6], and this remains our practice.

There are, however, many other aids which have been demonstrated to improve performance in the management of the acute abdomen, e.g. computer-aided diagnosis[7,8], fine catheter aspiration cytology of the peritoneal cavity[9], ultrasonography[10,11], peritoneal lavage[12] and microwave thermography[13]. There can be little argument with the results produced by computer-aided diagnosis over the last 15 years. Not only can diagnostic accuracy be improved by 10–20 per cent[8,14] but when used in the accident and emergency department fewer patients are admitted to hospital[8,15]. Nevertheless, there has been reluctance to accept computer aided diagnosis for a variety of reasons[16]. These studies bring into question the whole principle behind the management of the acute abdomen. There are two pathways of management: one pathway is to reach a diagnosis from which subsequent management decisions can be based (this could be termed a clinicopathological diagnosis); the other pathway is making a clinical decision; does the patient require an operation or not (this could be termed a procedural diagnosis) In the management of the acute abdomen it is our opinion that surgeons focus intuitively more on the procedural than on the clinicopathological diagnosis.

To investigate this hypothesis we compared the outcome of a procedure-based management strategy that incorporated selective laparoscopy with a hypothetical strategy based on diagnostic probabilities.

Patients and methods

All patients with acute abdominal pain of less than 1 week duration, who were admitted to hospital under one surgical firm, were studied over a period of 21 months. Patients were referred directly from their local general practitioner or from the casualty officer and assessed in the emergency department by the duty surgeon (senior house officer/registrar). All patients were classified after emergency investigations into one of four groups (*Table 1*) within 6 h of admission according to the perceived need for urgent operation The emergency investigations included blood tests, X-rays and urine microscopy In normal instances when a clinician is uncertain whether an operation is required a 'look and see' or 'wait and see' policy would normally be adopted. A decision was therefore made in group C about which pathway would normally be followed without laparoscopy and then these patients underwent laparoscopy Thus the influence of laparoscopy on management could be evaluated Not all patients with acute abdominal pain are suitable for laparoscopy (*Table 1*) and we therefore included the 'exclusion from laparoscopy group' (group D) The management decision in this group was studied in the same manner as for the other groups Thus all patients admitted with abdominal pain were studied Patients with abdominal trauma were excluded,

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Table 1 *Clinical decision groups*

Group	Decision
A	Requires an urgent operation
B	Does not require an urgent operation
C	Uncertain as to the need for urgent operation (including all women with possible appendicitis)
D	Ineligible for laparoscopy
	Contraindications
	Intestinal obstruction
	Previous abdominal surgery
	Severe cardiorespiratory disease
	Exclusions
	Acute pancreatitis
	Perforated viscus
	Renal tract disease
	Abdominal trauma
	Children

Table 2 *Management strategies based on computer-aided diagnosis*

	Examples	
	Probabilities (%)	Management decision
Patient 1		
Appendicitis	72	Operate
Non-specific abdominal pain	27	
Patient 2		
Non-specific abdominal pain	85	Observe
Appendicitis	11	
Diverticular disease	2	
Patient 3		
Cholecystitis	62	Either
Perforated peptic ulcer	35	
Dyspepsia	1	
Patient 4		
Intestinal obstruction	68	Either
Diverticular disease	31	

because we use peritoneal lavage as the first line of investigation in this group, children (less than 16 years of age) were also excluded because we did not have a paediatric laparoscope In addition, patients were excluded if a definite diagnosis could be made of acute pancreatitis (serum amylase concentration >1000 units/l), perforated viscus (free intraperitoneal gas visible on a standing chest X-ray) or renal tract disease (demonstrated by urine analysis, ultrasound or intravenous urography) as laparoscopy has little extra to offer here This does not mean that patients with these conditions did not enter the other three groups, only that their diagnosis could not be confirmed with certainty following the initial investigations.

For the second 11 months of the study classification continued as above but the patients' clinical details were collected on a structured data sheet after admission. Once the patient had been discharged the data were entered on to a BBC Master computer by a third party and analysed using a computer-aided diagnosis program[8]. A hypothetical management plan was then derived from the diagnostic probabilities produced. Examples are given in *Table 2*. There are several diagnoses that can be associated with the need for either early surgery or a non-operative approach, depending on the clinical condition of the patient; these include acute cholecystitis and intestinal obstruction. We therefore decided to consider that if either of these diagnoses was made both the decision to operate or the decision not to do so would be considered correct. We used computer-aided diagnosis probabilities rather than the clinician's diagnosis for two reasons: it is generally accepted that computer-aided diagnosis improves diagnostic accuracy by 10–20 per cent[8,14]; and it could not be influenced by subconscious or intuitive factors. No attempt was made to investigate the possible influence of computer aided diagnosis on clinical performance had the results been available to the clinician 'on the spot'.

Any patients whose final diagnosis suggested that they should have undergone surgery sooner or, alternatively, did not require surgery were considered as incorrect management decisions. Patients placed into group B (urgent operation not required) who went on to elective surgery (e.g. cholecystectomy for acute cholecystitis) were not considered as management errors All laparoscopies were performed under general anaesthesia in a standard fashion[1].

Statistical evaluation

Comparisons between the error rates before and after laparoscopy is logical but hypothetical. For this reason it can be argued that statistical comparisons of this type are invalid and therefore they have not been made in this paper. However, it is our view that they allow comparison of two independent methods of subdividing the sample (all those in group C) One method splits the group on the basis of the management policy if laparoscopy had not been available; the other divides the group on the basis of the outcome of laparoscopy. The former is an unfulfilled prospective scenario. The null hypothesis is that the real outcome and the scenario will not differ. This prospective scenario method is discussed in more detail elsewhere[17]. The incorporation of computer-aided diagnosis probabilities is out of temporal context and therefore no statistical comparisons were made.

Results

In the first phase 163 patients were studied (*Table 3*). Two patients in group A did not need surgery and three patients in group B should have undergone surgery earlier. The two unnecessary operations in group A were an appendicectomy for non-specific abdominal pain and an open and shut laparotomy for metastatic carcinoma of the stomach. In group B one patient with a diverticular abscess and two with acute appendicitis were incorrectly thought not to require surgery after initial assessment. There were two errors in the group excluded from laparoscopy (group D); the patients underwent appendicectomy and in both a normal appendix was removed. However, 14 patients in group C would have had incorrect management without laparoscopy but this was reduced to four by laparoscopy (one patient with retrograde menstruation had a pelvis full of blood at laparoscopy and a laparotomy was performed, in three patients the appendix could not be seen adequately and so appendicectomies were performed, two had non-specific abdominal pain and one had pelvic inflammatory disease). These results confirm those of our previous studies[1]: selective laparoscopy can reduce the overall error rate, in this case from 21 of 163 to 11 of 163.

In the second phase when the data sheet had been introduced, the overall error rate was three of 158 (*Table 4*), again improved from a potential figure of 11 of 158 by selective laparoscopy. The one error in group B was another patient

Table 3 *Phase 1: before introduction of the structured data sheet*

Group	*n*	Errors
A	16	2
B	57	3
C	37	4*
D	53	2
Total	163	11

* 14 before laparoscopy

Table 4 *Phase 2: after introduction of the structured data sheet*

		Errors	
Group	*n*	Clinical	Diagnostic (CAD)
A	24	0	0
B	55	1	6
C	35	0*	11
D	44	2	9
Total	158	3	26

* 8 before laparoscopy; CAD, computer-aided diagnosis

Table 5 *Errors in patients undergoing laparoscopy (Group C)*

Decision before laparoscopy	*n*
Phase 1	
Incorrect decision to 'look and see'	
Retrograde menstruation	1*
Non-specific abdominal pain	3 (2*)
Ruptured ovarian cyst	1
Incorrect decision to observe ('wait and see')	
Appendicitis	4
Torsion appendix epiploica	1
Small bowel obstruction (band adhesion)	2
Ectopic pregnancy	1
Bleeding ovarian cyst	1
Correct decision to observe	
Pelvic inflammatory disease (unnecessary appendicectomy after laparoscopy)	1*
Phase 2	
Incorrect decision to 'look and see'	
Pelvic inflammatory disease	2
Ruptured ovarian cyst	1
Incorrect decision to 'wait and see'	
Appendicitis	4
Ectopic pregnancy	1

* Incorrect decisions after laparoscopy: 4 of 72 (6 per cent)

with a diverticular abscess and the two errors in group D were again unnecessary appendicectomies.

The introduction of the structured data sheet improved the overall error rate from 11 of 163 in the first phase to three of 158 in the second phase. Overall 18 of 72 (25 per cent) patients who underwent laparoscopy avoided incorrect management decisions (*Tables 3* and *4*) and the clinical details and diagnoses of the errors in group C from both parts of the study are given in *Table 5*. A management strategy during this second phase based entirely on diagnostic probabilities, as produced by computer-aided diagnosis, would have resulted in an error rate of 26 of 158.

Discussion

This study formalizes what is known to all experienced clinicians about the management of the acute abdomen, namely that it is the recognition of which patients require early surgery that is the key to good clinical performance. However, there are still texts which place the emphasis differently, concentrating on attaining a clinicopathological diagnosis as a basis for action[18]. Our results reinforce the view that a procedural approach is more relevant.

The comparison that we made between the procedural attitude that we adopted and computer-aided diagnosis is 'unfair' to the latter It must be stressed that this study only compares two different management strategies, the one procedural-based and the other based on diagnostic probabilities. It makes no attempt to compare the influence computer-aided diagnosis would have had, if it had been incorporated into clinical practice with the results interpreted by the clinician on the spot. Although feasible to carry out, a formal prospective study that compares computer-aided diagnosis with laparoscopy-assisted decisions is complex. Therefore, computer-aided diagnosis was taken out of temporal context and arbitrary rules of interpretation of the diagnostic probabilities had to be used as a substitute for the clinician's incorporation of these into his decision about what to do. There is no doubt that computer-aided diagnosis improves diagnostic and procedural accuracy in the management of the acute abdomen[19–21]; however, it is well recognized that much of this change results from the use of a structured approach to data collection[8,22]. This study confirms the improvement in clinical performance associated with the use of a structured data sheet and has demonstrated that the same applies for procedural classification and laparoscopy. The final choice between using structured data collection with either computer ordering of diagnostic probabilities or selective laparoscopy is still open to the clinician. Both give excellent results. The marginal advantage of laparoscopy is that not infrequently it provides a precise diagnosis on which non-operative management can be based. However, the discipline, challenge and educational feedback imposed by computer-aided diagnosis should not be ignored[23].

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Anastomotic aneurysms of the femoral artery: aetiology and treatment

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The aetiology and treatment of 35 femoral false anastomotic aneurysms in 29 patients presenting over the 4-year period 1984–88 were reviewed retrospectively. The mean interval between primary anastomosis and false aneurysm repair was 6 years (range from 2 weeks to 16 years). Twenty-two (63 per cent) false aneurysms had occurred after previous aortobifemoral bypass grafting for occlusive aortoiliac disease. Seven (20 per cent) presented as acute surgical emergencies. Review of the records of the initial operations revealed that superficial wound infections with positive bacteriological cultures had been present in eight cases (23 per cent) and a further two (6 per cent) had lymph fistulae. Thirty-two false aneurysms were repaired, by simple reanastomosis in 14 cases, interposition grafting in 17 cases and in one case by complete revision to an aortobifemoral bypass graft. The risk of a further operative repair was less (P<0·05) following interposition grafting, than after simple revision. False aneurysm repairs, when compared with primary reconstructions done during the same period, were associated with more superficial wound infections (37 versus 10 per cent) and more explorations for haemorrhage within 30 days (19 versus 7 per cent).

Keywords: Anastomotic aneurysm, femoral artery

Despite their relatively low incidence (0·5–4 per cent)[1,2], non-infected anastomotic aneurysms continue to complicate arterial suture lines. Such aneurysms were thought to be due to fragmentation of silk sutures[3–6], but the change to synthetic non-absorbable sutures has not eliminated the problem. Risk factors are now thought to include excessive anastomotic tension[3,7–9], damage to the host artery wall by endarterectomy or suture-induced weakness[3,10–12], and alteration in the stress pattern across the anastomosis from underlying movements of the hip joint[13].

False aneurysms usually arise from weaknesses and disruption of the arterial wall adjacent to the anastomosis between the graft and the host artery. Blood escapes to form a communicating haematoma which is limited in size by the surrounding tissue. Although the interior of the false aneurysm sac contains thrombus and is usually lined by endothelial cells, there is an absence of medial and adventitial layers.

The femoral region is by far the most common site for anastomotic aneurysms. Satiani[14], in a collective review, reported that 79 per cent of 444 anastomotic aneurysms occurred in this region. Of 20 anastomotic aneurysms reported from Nottingham[15], 80 per cent were in the groin, but no site of an arterial anastomosis is exempt. Anastomotic aneurysms are much more common at the distal end of aortofemoral grafts than aortoiliac grafts, suggesting that local factors including hip flexion and excessive tension may have a role.

Patients and methods

Twenty-nine patients (27 male and 2 female patients) with 35 non-infective femoral false aneurysms secondary to arterial anastomosis in the groin were identified in a 4-year period between September 1984 and September 1988 inclusive. Primary and mycotic aneurysms, and false aneurysms from diagnostic femoral arterial cannulation and from intra-arterial injection by drug addicts were excluded. The diagnosis of false aneurysm was made on clinical grounds with confirmation by ultrasound and arteriography where indicated.

The false aneurysms repaired represented 4 per cent of 765 femoral artery anastomoses done during the period of study. The mean interval between primary arterial suture to false aneurysm repair was 6 years, with a range of 2 weeks to 16 years (*Figure 1*). Some original bypass and aneurysm operations were done elsewhere. Full details of the primary reconstruction were available from the case notes in 31 (88 per cent) and the remainder were obtained from other hospitals' notes and general practitioner reports. Other data recorded included age, sex and atherosclerotic risk factors.

Results

Primary reconstructive operation

The indications for the primary reconstructive procedures had been occlusive peripheral arterial disease in 29 (83 per cent) cases and aortoiliac aneurysm in six (17 per cent) cases. Twenty-two (63 per cent) false aneurysms occurred after aortofemoral bypass and eight (23 per cent) after iliofemoral bypass, with the remaining five (14 per cent) having occurred after a variety of other operations (*Figure 2*). Twenty-eight (80 per cent) were detected during routine follow-up and seven (20 per cent) presented as acute surgical emergencies, five (14 per cent) having ruptured and two (6 per cent) having thrombosed.

Six patients had bilateral anastomotic aneurysms at presentation and five (14 per cent) aneurysms had recurred at the same site following an earlier repair. Seven patients were hypertensive, none was diabetic and five had undergone more

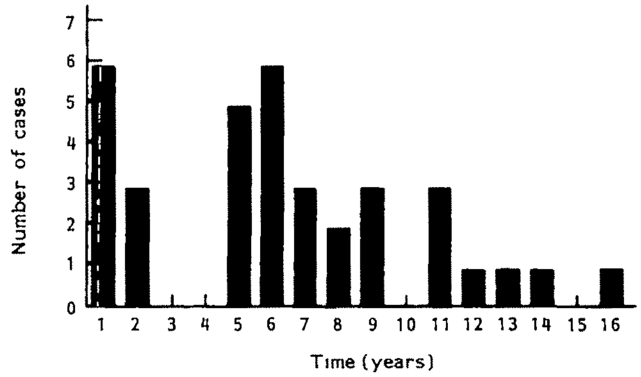

Figure 1 *Interval (years) between primary operation and false aneurysm formation (35 cases)*

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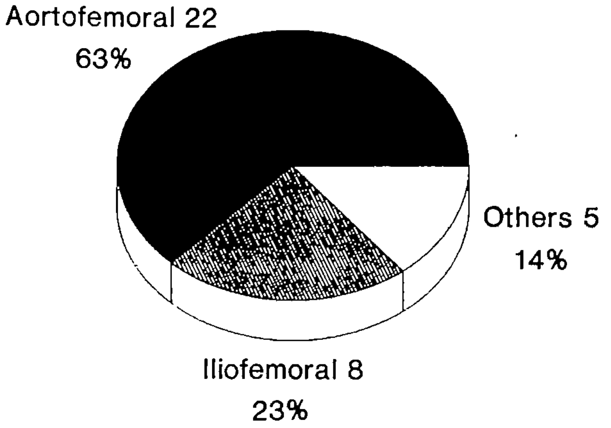

Figure 2 *Nature of primary operation in 35 cases of false aneurysm*

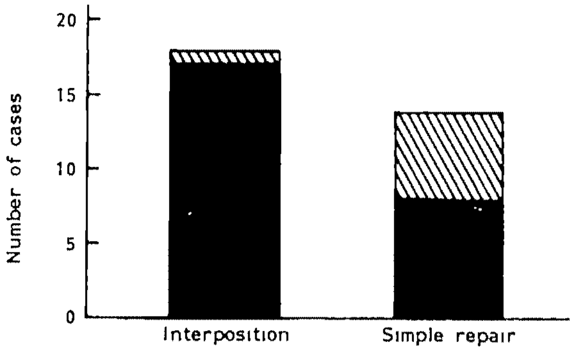

Figure 3 *Need for further revision after operation for false aneurysm by interposition grafting or simple repair* ■, *good*, ■, *revised*

than one groin exploration before developing a false aneurysm, e.g. an iliofemoral bypass revised to an aortobifemoral bypass In five (14 per cent) instances a femoral endarterectomy had also been performed at the time of the original bypass, and this may have weakened the arterial wall. Silk sutures were found in four cases and polypropylene had been used in the remainder.

A review of the records revealed that superficial wound infections with positive bacteriological cultures had been present in eight (23 per cent) lesions and a further two (6 per cent) had lymph fistulae. All patients who had had their primary operations in Bristol had received intravenous cephalosporin prophylaxis at the induction of anaesthesia. The type of graft that had been used at the original bypass was woven Dacron® (du Pont) in 17 (49 per cent) of the 35 cases and knitted Dacron in eight (23 per cent). The operating records in the remaining ten (29 per cent) cases did not distinguish between the two types.

Management of false aneurysms

All but three of the 35 false aneurysms were repaired surgically Of these three, two are small and in unfit patients, and one is asymptomatic, small and situated on the opposite side to a recently repaired anastomotic aneurysm. At exploration all the false aneurysms were found to be localized to the inguinal region with no extension above the inguinal ligament.

Technique of operative repair

Following aneursysmectomy, the method of revision was simple reanastomosis in 14 (44 per cent) cases and interposition grafting in 17 (53 per cent) cases. One aortounifemoral graft was revised to an aortobifemoral bypass Five interposition grafts were covered by the sartorius muscle to help prevent lymph fistulae.

Revision after simple and interposition repair

To date, six of the simple direct repairs have required further revision, five for recurrence of false aneurysm and one for thrombosis (*Figure 3*) This compares unfavourably with only one further revision for thrombosis in the interposition graft group (χ^2 with Yates' correction = 4·075; $P<0·05$). This suggests that the risk of a further operative revision being required is less with an interposition graft than with simple revision, despite the treatment option being decided by the surgeons' preference and not by randomization.

Healing following false aneurysm repair

In comparison with primary reconstructions done during the period of the study, false aneurysm repair was associated with an increased risk of postoperative complications: these included re-exploration for haemorrhage within 30 days of surgery (19 *versus* 7 per cent), and superficial wound infections (37 *versus* 10 per cent).

Discussion

There has been much controversy over the aetiology of anastomotic aneurysms of the femoral artery, with excessive anastomotic tension, superficial wound infection and hypertension as suggested causative factors. It seems likely that a degenerative process in the arterial wall at the suture line may cause separation of the host vessel from the prosthesis. Despite many authors finding intact suture on the grafts[3,11,16,17], dense fibrosis around the aneurysmal sac can make an accurate operative assessment of the anatomy very difficult We found no evidence of weakness in any of the grafts[18,19], although some dilatation of knitted grafts was noted[20]. Our data were insufficient to confirm or refute reports implicating previous endarterectomy[3,11,16]. The suggestion that local wound complications, including haematoma, lymph fistula and superficial wound infection[7,10,12,21,22] may lead to a ten-fold[23] increased chance of false aneurysm was supported in this study, although we could not confirm a recent report that superficial infection leads to a quicker destructive rate than sound healing without delay[12]. The risk of false aneurysm was not increased in hypertensives compared with normotensives, confirming the results of a Viennese study[12] and contrary to frequent assertions[1,2,11,14,16,21].

Poststenotic dilatation as a cause of false femoral aneurysm formation, due to the impingement of the common femoral artery on the inguinal ligament, has been reported[24] The inguinal ligament had been divided at the original reconstruction to avoid graft tethering but this procedure was not performed in any of our cases.

Our results favour the use of an interposition Dacron graft rather than simple reanastomosis as the treatment of choice because the latter is associated with an increased risk of a further false aneurysm[23]. Excessive anastomotic tension seems to be the most likely explanation of false aneurysm formation, as there have been no recurrent false aneurysms following the use of an interposition graft. Mechanical stresses in the region of the hip joint and tension in the direction of the graft axis expose the anastomosis to high shearing forces and this may also cause disruption of the Dacron–artery suture line. It is possible that false aneurysms may form early in the postoperative period if they are related to a local technical problem, e.g. a weak arterial wall, excessive tension, or wall damage from sutures. Teeuwen *et al.*[25] have recently demonstrated five anastomotic aneurysms in 234 aortic Dacron replacements within 3 weeks of bypass using intravenous digital subtraction angiography.

A reliable comparison with patients who had a similar bypass, but who have not developed a false aneurysm would be desirable, but it was difficult to find a matching operated population going back for 16 years. This is currently a subject under review using a prospective computerized vascular audit.

In conclusion, we suggest that careful follow-up after primary arterial reconstruction continues to be advisable, as false aneurysms left untreated can lead to complications. Only in small, asymptomatic, static cases, in high risk patients, should a conservative policy be used. To help minimize the risk of developing an anastomotic false aneurysm, scrupulous care must be taken at the initial reconstruction to avoid superficial wound infection. The graft should be free from tension and as generous amounts of artery wall as possible should be incorporated in the suture line. Femoral anastomotic aneurysms are best treated by interposition Dacron grafting rather than by direct repair.

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Short note

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Intervention for graft stenoses: the role of surgery and transluminal angioplasty

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Femorodistal grafts have a high rate of failure in the first 2 years after operation[1], and the rapid development of stenoses in such grafts seems to be a prime cause[2]. The development of non-invasive techniques, such as ankle:brachial pressure indices and duplex scanning, permits intensive surveillance and identification of grafts at risk at an early stage[3–5]. Appropriate intervention can then be planned before graft thrombosis can occur. Since 1985, all patients undergoing femorodistal reconstruction in this unit have been followed prospectively. The results of intervention for graft stenosis are presented and the role of percutaneous transluminal angioplasty is debated.

Methods

Patients were reviewed in the vascular laboratory 6 weeks after operation and, thereafter, at 3-monthly intervals or more regularly, if indicated. The techniques used, which have been described before[3], included clinical assessment, measurement of ankle:brachial pressure indices before and after stress, and duplex ultrasonography of the graft. Digital subtraction angiography was performed for clinical deterioration, a fall in the ankle:brachial pressure index of >0.2, or a haemodynamically important stenosis detected by duplex scanning. Proximal stenoses were treated by formal surgical revision (jump graft or patch angioplasty), and intragraft or distal anastomotic stenoses were treated by percutaneous transluminal angioplasty using an antegrade puncture. Sustained high pressures (12–15 atm for 5 min) were often required to dilate graft related stenoses successfully. An initial technical success rate of 100 per cent was confirmed by angiography and duplex ultrasonography. There were no cases of anastomotic disruption or false aneurysm formation.

Results

Two hundred and six femorodistal reconstructions were performed during the 15-month period ending in January 1987. In 105 reconstructions *in-situ* vein was used, 98 used prosthetic material, two used reversed vein and one used umbilical vein. The large number of prosthetic grafts reflected a preference for synthetic material for above knee reconstructions in order to preserve the long saphenous vein for more distal bypass or coronary artery surgery.

Twenty-two stenoses were identified in vein grafts, at a mean of 8 months after operation. Nineteen were treated immediately because of deteriorating ankle:brachial pressure indices or because they were high grade (>75 per cent diameter) according to duplex derived velocity criteria. Of these 19 patients 17 were asymptomatic. Three stenoses, causing a fall in pressure index of <0.2 or that were low grade according to duplex criteria, were observed, but all progressed far enough to require revision within 3 months of first identification.

Of six proximal anastomotic stenoses treated by formal revision, five remained satisfactory at 15 months follow-up. One graft occluded 16 months after revision. Following successful transluminal angioplasty, nine distal anastomotic lesions were kept under close surveillance; all recurred within 6 months. Of seven similarly treated intragraft stenoses, six recurred within 6 months. One intragraft lesion, however, remained satisfactory after 18 months follow-up.

Discussion

Haemodynamically important graft stenoses can now be rapidly identified using non-invasive techniques[3–5], especially with the advent of colour coded duplex ultrasonography. High throughput and low cost per patient make this an economical approach. As most graft stenoses occur in the first 3 years after surgery, it would not appear necessary to employ such follow-up indefinitely.

The most appropriate treatment for graft stenosis remains in doubt. Percutaneous transluminal angioplasty is attractive because of its ease and simplicity, but our experience has been disappointing as restenosis seems almost universal and rapid. The reasons for this are unclear but it is recognized that infrainguinal angioplasty yields lower long term patency rates than aortoiliac angioplasty[6,7]. More importantly, the type of lesion within a graft differs from atherosclerotic plaque, which is amenable to fracture and remodelling[8]. Early graft stenosis is presumably caused by fibrosis or anastomotic neointimal hyperplasia. Dilatation of a fibrotic lesion may exacerbate fibrosis, and does nothing to prevent the progression of intimal hyperplasia. Because of this and our current experience, we conclude that a randomized trial of surgical revision and percutaneous transluminal angioplasty is needed to determine the best method of 'graft maintenance'.

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Abdominal aortic aneurysm repair in the over eighties

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Between January 1980 and September 1988, 34 octogenarians underwent aortic aneurysm repair. There were 26 men and eight women with a median age of 83 years (range 80–88 years). Twenty underwent 'emergency' repair after presenting with pain and/or collapse: 11 with a retroperitoneal rupture, three with an intraperitoneal rupture and six with an expanding aneurysm. The mortality rate for this group was 35 per cent. During the same period 14 patients had an elective repair and there were no deaths within 30 days. The mean hospital stay for the elective group was 14·2 days compared with 17·0 days for survivors in the emergency group. There was no significant difference in terms of risk factors between those who developed postoperative complications and those who did not. These mortality rates compare favourably with our overall mortality results for elective (4·6 per cent) and emergency (31 per cent) surgery. Those patients over 80 years of age with infrarenal abdominal aortic aneurysms should not be refused surgery on the basis of age alone; each patient should be judged individually.

Keywords: Aortic aneurysm, octogenarian

Surgical repair of aortic aneurysm in the elderly has been a controversial issue in recent years and has been highlighted in the UK by the recent Confidential Enquiry into Perioperative Deaths (CEPOD)[1]. This suggested that patients over 80 years of age with ruptured abdominal aortic aneurysm are unlikely to survive surgery and, therefore, should not be operated on.

Elderly aneurysm patients are known to tolerate blood loss poorly and concurrent systemic disease, such as coronary heart disease, causes an increased risk of perioperative complications[2]. Nevertheless, improvements in anaesthetic and surgical technique have reduced morbidity and mortality and have led to an improved outcome in high risk groups, including the elderly. Ammar reported a mortality rate of 7·8 per cent for elective aneurysm repair in patients over 80 years old, which compared favourably with his statistics for those under 80 years[3]. Selection of patients for surgery in the older age group has to take into account physical factors such as coronary heart disease as well as social and psychological factors. The older age group may include patients who have a poor quality of life owing to mental or physical handicap, from being wheelchair bound or from coexistent malignant disease. Although all these can be present in those under 80 years of age, they are more common in the older age group.

The increased awareness of the medical profession to the risks of abdominal aortic aneurysm, and the development of ultrasound as a diagnostic tool have resulted in an apparent increase in the incidence of the condition[4,5]. As the general population ages, more octogenarians will present with abdominal aortic aneurysm. The purpose of this study was to examine the mode of presentation, treatment and outcome of patients over 80 years of age with infrarenal abdominal aortic aneurysm.

Patients and methods

Details were obtained of all infrarenal abdominal aortic aneurysm repairs carried out at the Bristol Royal Infirmary between the years of 1980 and 1988. For the first 4 years case notes were used but from September 1984 the details were obtained from a prospective computerized vascular audit. Thirty-four octogenarians (age range 80–88 years, with five patients over 85 years of age) underwent operation out of an overall total of 311 patients undergoing aortic aneurysm repair. Patients were divided into two groups, 'elective' and 'emergency'. The emergency group consisted of (1) 'expanding aneurysms' (patients presenting with severe pain but no extravasation of blood at operation); (2) retroperitoneal rupture; and (3) intraperitoneal rupture. Using a computerized audit system the following details were recorded: risk factors, presentation, general and surgical complications, mortality and cause of death, and length of hospital stay

Results

Of the 34 octogenarians undergoing aortic aneurysm repair, 26 were men and eight were women, with an age range of 80–88 years. Of these, 20 underwent emergency and 14 elective repair (*Figure 1*). There were no cases of inflammatory aneurysm or of horseshoe kidney. It was not possible to obtain details of how many octogenarians were not offered surgery because their general practitioner did not refer them or because the surgeon felt that surgery was inappropriate. All patients who arrived in the accident department alive were transferred immediately to theatre. No patient could be identified who was refused surgery at this stage. There were no reports to the coroner during the study period of any deaths in the community due to ruptured aortic aneurysm in this age group, although it is inevitable that some who died of ruptured aneurysm were not reported. Alternatively, the cause of death may have been ascribed to some other pathology such as myocardial infarction.

Of the 14 elective repairs nine were in asymptomatic patients and five were in symptomatic patients, all of whom complained of back pain. All 14 patients with elective repairs left hospital alive; there were no deaths within 30 days of operation. This compared with a mortality rate in our overall elective series of 4·6 per cent.

Of the 20 patients undergoing an emergency repair six had expanding aneurysms with no evidence of rupture, 11 were retroperitoneal ruptures, and three were intraperitoneal rupture (*Figure 1*). Seven of the 20 octogenarians undergoing emergency repair died (*Table 1*). This mortality rate of 35 per cent compares favourably with that of 31 per cent for all emergency repairs (116 patients) over the same time period. One patient, who died during surgery, presented with an intraperitoneal rupture and an aortocaval fistula; he had had his aneurysm wired 12 years previously. One patient died in oliguric renal failure 2 weeks after a massive perioperative blood transfusion. Another died 2 days after operation from renal failure, having sustained several hours of hypotension during transfer from

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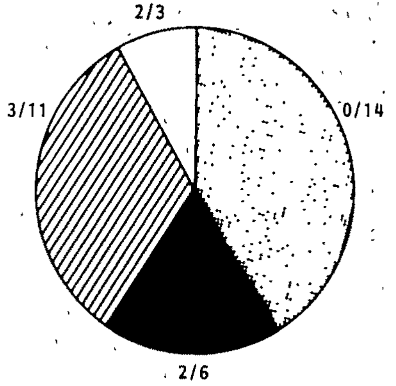

Figure 1 *Presenting features in octogenarians with abdominal aortic aneurysms. The fractions represent deaths/total number of patients in each group* □, *elective group;* ■, *patients with expanding aneurysms;* ■, *patients with retroperitoneal rupture,* □, *patients with intraperitoneal rupture*

Table 1 *Cause of death in seven octogenarians undergoing emergency aneurysm repair*

Cause of death	No. of patients
Peroperative haemorrhage	2
Renal failure	2
Myocardial infarction	2
Adult respiratory distress syndrome	1

another hospital 20 miles away. Two patients died from myocardial infarction several days after an apparently uncomplicated operation. One patient, who presented with an intraperitoneal rupture, died on the day of operation from disseminated intravascular coagulation and another patient developed adult respiratory distress syndrome and died on the 12th day after surgery.

Risk factors were as follows: four patients were hypertensive, four suffered from coronary heart disease and three had renal impairment. However, there was no significant correlation between the presence of cardiovascular risk factors and subsequent postoperative morbidity and mortality. Postoperative complications occurred in 14 patients. The commonest complication was chest infection, occurring in eight of the 27 survivors. The average hospital stay for all patients undergoing elective operation was 14·2 days, while for the survivors of emergency procedures it was 17·0 days.

The most common repair was with a straight Dacron® (du Pont) graft, which was used in 18 out of 20 (90 per cent) emergency procedures. In one case a bifurcated graft was used for a retroperitoneal rupture in which the aneurysm involved the common iliac arteries. One patient died before a prosthesis was sewn in. In the elective cases, bifurcated grafts were used on six occasions (42 per cent); two of these patients had iliac artery aneurysms. A knitted prosthesis was used on only two occasions, and no polytetrafluoroethylene grafts were inserted.

Discussion

Our study provides results comparable to those from previous work elsewhere. In a series of 86 octogenarians, O'Donnell reported an overall mortality rate for a non-ruptured group of 4·7 per cent, with a 74 per cent mortality rate for a ruptured group[6]. In contrast Esselstyn reported a higher elective mortality rate of 14 per cent in 152 patients aged 75 years and above, compared with an overall 9 per cent mortality rate. Of his 'emergency' patients 63 per cent died[7]. Sterpetti divided patients into high and low risk groups according to the number and severity of associated risk factors. In the high risk group, the operative mortality rate was 39·8 per cent compared with 4·3 per cent in the low risk group[8]. He adopted a policy of serial ultrasound follow-up on patients with small aneurysms but observed that although operative mortality in high risk patients may be high, a large aneurysm left alone is a constant threat to life. Edmunds recommended resection in octogenarians only for ruptured, expanding or newly symptomatic aneurysms[9], but this policy may lead to a higher risk of operative mortality than offering resection on an elective basis, especially in those patients with large aneurysms.

Bjerkelund showed that coronary heart disease and renal failure were the most important risk factors[2]. Szilagyi[10] observed that arterial hypertension was associated with subsequent aneurysm rupture and suggested that hypertensives should not be excluded from surgery on the basis of blood pressure alone. In our series, four patients were hypertensive and four had coronary heart disease but the presence of these risk factors was not significantly associated with subsequent morbidity or mortality.

Fourteen out of the 27 survivors had one or more general complications, most commonly a chest infection. This compares with the postoperative complication rate of 54 per cent described by Treiman *et al.*[11]. All of their patients had undergone elective aneurysmectomy.

An argument put forward against operating on octogenarians with aneurysms relates to their relatively short postoperative life expectancy. O'Donnell compared three groups of patients with aneurysms who were over 80 years of age with octogenarians without aneurysms. The survival curve for those undergoing elective surgery matched that of the general population, while that for the ruptured group showed an initial sharp decline followed by a more gradual decline over the months after successful surgery. Patients with aneurysms not treated by elective surgery had a much shorter life expectancy than that of the general population. Szilagyi studied a group of patients who were not offered aneurysmectomy due to a variety of complications (patients over 80 years of age were generally excluded). Of these unoperated patients, 27·8 per cent died from a ruptured abdominal aortic aneurysm over a 20-year follow-up period, this being the second commonest cause of death after coronary heart disease in his series. Szilagyi observed that with advancing age other degenerative diseases contributed to a reduced life expectancy, as well as operative mortality. However, advanced age accounted for only 12 per cent of operative contraindications in his series, confirming O'Donnell's findings that age *per se* was only of prognostic significance when expressed in physiological rather than chronological terms.

In our current series the ratio of emergency to elective aneurysm repairs increased with age. This may reflect the referring practices of the local general practitioners who may not screen the older age group or refer them for a surgical opinion. This observation is supported by the work of Petracek[12] who found that 51 per cent of primary health care physicians said they would not refer octogenarians with abdominal aortic aneurysms for consideration for surgery. He suggested that these physicians had made an incorrect assessment of operative risk in this age group.

Our results show that in a selected group of octogenarians the operative mortality and morbidity rates were similar to those in non-octogenarians. It is more cost-effective to operate electively rather than as an emergency. Size is not necessarily a good guide to impending rupture[8] and so all octogenarians with an infrarenal abdominal aortic aneurysm should be considered for surgery, although it is probably safe to keep under observation any aneurysm less than 4·5 cm in diameter[13].

In summary, this review of octogenarians undergoing surgery for aortic aneurysm over the last 8 years shows that the results in both elective and emergency repair compare favourably with our overall results and with the results of other series. We conclude that the CEPOD recommendation not to operate on octogenarians with ruptured aneurysms is unjustified and that all patients should undergo the same selection criteria for operation regardless of age.

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Acute lower limb arterial ischaemia: a role for continuous oxygen inhalation

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Simultaneous readings of transcutaneous partial pressure of oxygen (P_{tc,O_2}) *were obtained from the left anterior chest wall, from 10 cm distal to the medial aspect of the knee joint, and from the first dorsal webspace in 16 patients with acute peripheral arterial ischaemia of the leg. Oxygen was administered at concentrations of 24, 40, 60 and 100 per cent. Mean(s.d.) initial chest* P_{tc,O_2} *(53 (17) mmHg) was significantly higher than that of the medial lower limb site (37(17) mmHg). After inhalation of 24 per cent oxygen, a statistically significant* ($P<0\cdot025$) *increase in chest* P_{tc,O_2} *was achieved (63(20) mmHg), but the increase in* P_{tc,O_2} *(43(19) mmHg) at the medial lower limb site was not statistically significant. Inhalation of 40 per cent oxygen resulted in significant increases at both sites (chest: 83(23) mmHg,* $P<0\cdot01$*; limb: 53(26) mmHg,* $P<0\cdot05$*).* P_{tc,O_2} *in the limb at this concentration of inhaled oxygen was equal to the initial chest level. Increasing the oxygen concentration to 60 per cent and then to 100 per cent produced further significant* ($P<0\cdot001$) *increases in* P_{tc,O_2} *at both sites. The use of continuous oxygen inhalation during acute ischaemia may improve tissue nutrition before, during and after definitive treatment.*

Keywords: Transcutaneous oxygen, acute arterial ischaemia

Transcutaneous partial pressure of oxygen (P_{tc,O_2}) measurements have been shown to be useful in the assessment of amputation level[1,2] and in the determination of the severity of arterial ischaemia[3–7]. In the management of acute arterial ischaemia the distinction between thrombosis and embolism and the severity of that ischaemia determine the type and timing of intervention. In the case of embolism this will be in the form of balloon embolectomy[8] or high dose heparin therapy[9]. Patients with acute thrombosis will require surgical reconstruction[10] or thrombolysis, in an attempt to achieve limb salvage[11–13]. In these patients few additional therapies to reduce tissue damage are of proven value. Some authors advocate heparin to reduce the risk of propagation of the thrombus which may make surgery or thrombolysis more difficult[9,10]. However, the role of continuous oxygen therapy has not been addressed. Administration of 100 per cent oxygen has been shown to produce significant increases[14] in limb P_{tc,O_2}, but this is obviously impractical as a continuous therapy. As part of our assessment before consideration of thrombolytic therapy, we have evaluated the effects of a range of inhaled oxygen concentrations on the P_{tc,O_2} of the lower limb in 16 patients with acute peripheral arterial ischaemia of the leg.

Patients and methods

Sixteen patients with acute peripheral arterial ischaemia of the leg were studied. There were 14 men and two women with a mean(s.d.) age of 72(9) years The mean(s d.) ankle:brachial systolic index was 0 12(0 17), and nine patients had inaudible ankle Doppler ultrasound signals. Eight patients had rest pain alone and eight had rest pain and gangrene. Three patients were diabetic. Seven patients had diminished or absent sensation in the affected limb, usually confined to the dorsum of the foot No patient had motor paralysis. The mean(s.d.) duration of acute ischaemia was 14(10) days

P_{tc,O_2} readings were made using a Radiometer Dual Channel TCM2 (Radiometer, Coventry, UK) with standard platinum electrodes. Both electrodes were calibrated before each recording. Three sites were assessed: left anterior chest wall, 10 cm distal to the line of the medial aspect of the knee joint, and the first dorsal web space on the affected limb Readings were obtained simultaneously from the chest wall and the dorsum of the foot or lower limb. All patients were rested supine, to allow equilibration for 30 min before obtaining baseline P_{tc,O_2} readings. Baseline P_{tc,O_2} was then assessed at each site with the electrode temperature set at 44°C. A stable reading was confirmed by a plateau on the chart recorder and a constant heat output Oxygen was then administered via a face mask with variable venturi connectors to achieve oxygen concentrations of 24, 40 and 60 per cent according to the manufacturers guidelines (Controlled Percentage Kit, Intersurgical Complete Respiratory Systems, Twickenham, UK). A closed circuit, incorporating a non-return valve in association with a Waters' bag (Ohmeda, Harlow, UK), was used to administer 100 per cent oxygen via a standard anaesthetic face mask. The maximum plateau reading was recorded for each oxygen concentration before increasing the concentration to the next level All patients gave informed consent.

Results are expressed as mean(s.d.) unless otherwise specified Statistical analysis was performed using the Mann–Whitney *U* test.

Results

Initial anterior chest P_{tc,O_2} (mean(s.d.) 53(17) mmHg) was significantly higher than that from the medial lower limb site (37(17) mmHg, $P<0\cdot025$), and from the dorsum of the foot (1(3) mmHg, $P<0\cdot0001$; *Table 1*). After inhalation of 24 per cent oxygen, significant increases ($P<0\cdot025$) in chest P_{tc,O_2} were achieved (63(20) mmHg) but only minimal increases in medial lower limb P_{tc,O_2} (43(19) mmHg). Inhalation of 40 per cent oxygen resulted in significant increases at both sites (chest: 83(23) mmHg, $P<0\cdot01$; medial lower limb: 53(26) mmHg, $P<0\cdot05$). At this point P_{tc,O_2} in the limb was equal to the initial chest level. Increasing the oxygen concentration to 60 per cent and then to 100 per cent produced further significant ($P<0\cdot001$) increases in P_{tc,O_2} at both sites (*Figures 1* and *2*) However, at the dorsal foot site administration of even 100 per cent oxygen failed to produce a consistent increase in P_{tc,O_2}. Lower levels of oxygen concentration were not assessed at this site.

The oxygen perfusion index (OPI) was calculated as follows:

$$\mathrm{OPI}=\frac{P_{tc,O_2}\ \text{limb on } O_2 \text{ (at specified concentration)}}{P_{tc,O_2}\ \text{initial chest (on air)}}$$

This allows an assessment of the improvement in peripheral tissue oxygenation following oxygen administration, compared with the maximum resting tissue perfusion for that patient (i.e over the chest wall). There is a significant increase in this index

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Table 1 *Transcutaneous partial pressure of oxygen at three sites, and oxygen perfusion index, following inhalation of varying oxygen concentrations*

		Oxygen concentration (%)			
Site	Air	24	40	60	100
Chest (mmHg)	53(17)	63(20)*	83(23)†	116(33)‡	271(59)‡
Medial lower limb (mmHg)	37(17)	43(19)	53(26)*	68(36)‡	136(83)‡
Dorsum of foot (mmHg)	1(3)	—	—	—	10(23)
Oxygen perfusion index	0·73(0·32)	0·84(0·36)	1·05(0·52)*	1·36(0·72)†	2·76(1·79)‡

All values are mean(s.d.), * $P<0·05$, † $P<0·01$, ‡ $P<0·001$ (Mann–Whitney U test: comparisons with respective result on air)

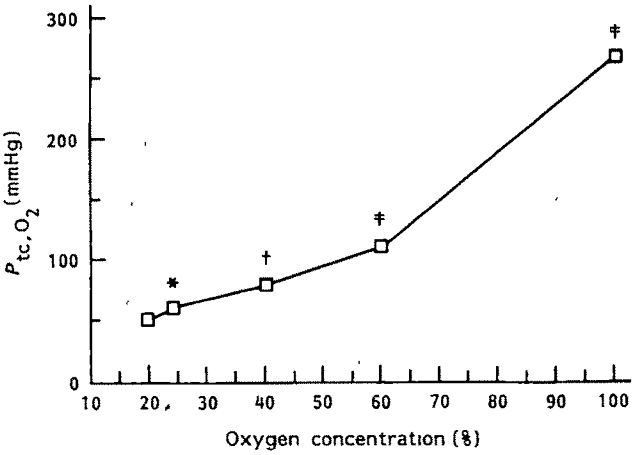

Figure 1 *The effect of concentration of inspired oxygen on the transcutaneous partial pressure of oxygen* (P_{tc,O_2}) *over the anterior chest wall site* * $P<0·05$, † $P<0·01$, ‡ $P<0·001$ (*Mann–Whitney* U *test*)

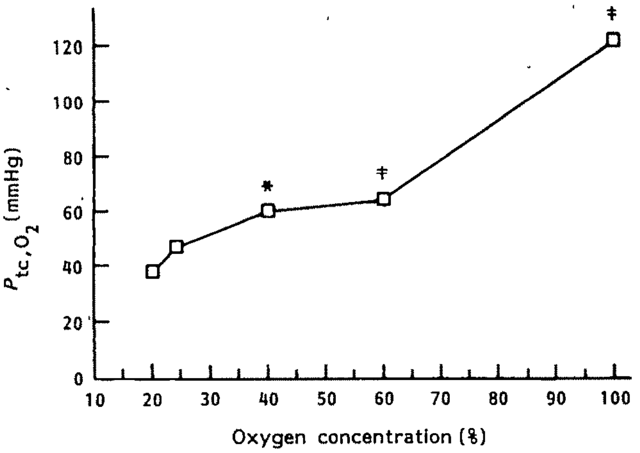

Figure 2 *The effect of concentration of inspired oxygen on the transcutaneous partial pressure of oxygen*(P_{tc,O_2}) *over the medial lower limb site.* * $P<0·05$, ‡ $P<0·001$ (*Mann–Whitney* U *test*)

using 40 per cent oxygen ($P<0·05$), with further increases using 60 and 100 per cent oxygen (*Figure 3*).

Discussion

Despite using an electrode temperature of 44°C, marked individual differences in P_{tc,O_2} undoubtedly still occur due to variability in skin thickness and vascularity[15,16]. Initially, P_{tc,O_2} was thought to correlate with arterial oxygen tension[17,18] but later studies showed it to correlate with oxygen delivery[19–23]. This may explain the failure of increased concentrations of inspired oxygen to enhance P_{tc,O_2} at the dorsal foot site. With extremely low blood flow in an ischaemic foot, blood may be diverted away from skin capillaries, hence any rise in blood oxygen content may be already taken up by the time that blood reaches skin capillaries. Attempts to improve the ability of transcutaneous oxygen monitors to differentiate disease states or to predict healing at amputation levels has involved the use of positional changes[24], regional perfusion indices[25], exercise stress testing[26], postischaemic hyperaemia[5] and the rate of rise of P_{tc,O_2} following inhalation of 100 per cent oxygen[14].

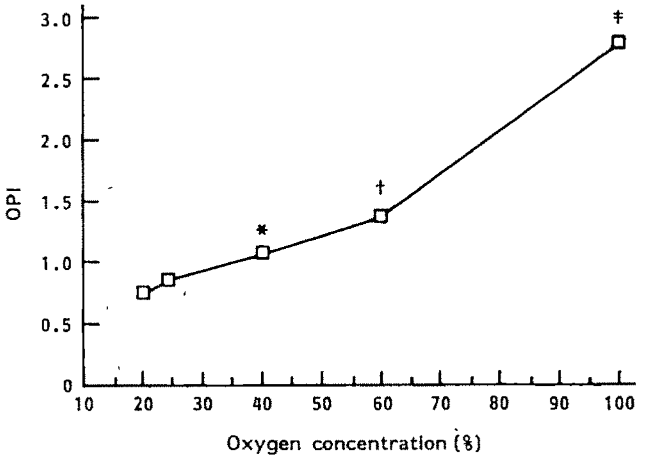

Figure 3 *The effect of concentration of inspired oxygen on the oxygen potential index (OPI).* * $P<0·05$, † $P<0·01$, ‡ $P<0·001$ (*Mann–Whitney* U *test*)

There is a large increase in P_{tc,O_2} following 100 per cent oxygen administration but this is obviously not a practical proposition for continuous use. However, our study has shown that even with 24 per cent oxygen an increase in P_{tc,O_2} is seen, which becomes statistically significant in the compromised limb using 40 per cent oxygen. Furthermore, the oxygen perfusion index using 40 per cent oxygen had a mean value of 1·05. In other words, the P_{tc,O_2} in the lower limb is significantly higher than the probable maximum resting P_{tc,O_2} in that patient. Administration of 60 per cent oxygen produced a further significant increase in P_{tc,O_2} over the anterior chest wall ($P<0·001$), but it did not produce a commensurate increase at the medial lower limb site ($P>0·05$).

The mean(s.d.) initial chest value in our study (53(17) mmHg) is lower than might be expected. Although increasing age is known adversely to affect P_{tc,O_2}[27], the mean(s.d.) age of our patients was 72(9) years and one might have expected a mean P_{tc,O_2} of approximately 75 mmHg. The low value obtained may reflect the generalized nature of arterial disease in our patients, with associated cardiorespiratory insufficiency.

Although the oxygen concentrations are quoted as 24, 40, 60 or 100 per cent, we readily admit that the actual oxygen concentrations received by the patients were probably less than these. Nevertheless, the experiment reflects clinical practice and we believe the results are clinically valid. We did not perform simultaneous arterial partial pressure of oxygen measurements as the patients were due to receive thrombolytic therapy.

There are several clinical situations in which continuous oxygen may be of help. In patients with ischaemic ulcers, we may be able to accelerate healing by increasing local oxygen concentration[28]. Distal tibial revascularization is also associated with reduced skin oxygenation for up to 7 days after surgery[29,30] and oxygen therapy may be of benefit. Patients with ischaemic rest pain obtain some relief from their symptoms by hanging the leg outside the bed. In the dependent position an increased $P_{\mathrm{tc,O_2}}$ at the foot is seen[24] which could be further augmented by oxygen inhalation.

Adjunctive therapy with continuous oxygen inhalation may help to protect ischaemic tissues while awaiting definitive intervention or during peripheral arterial thrombolysis. It could also be used in the early postoperative period after amputation to aid wound healing[31]. Although significant elevation of $P_{\mathrm{tc,O_2}}$ was seen at the medial lower limb site rather than over the dorsum of the foot, adjunctive therapy may still be of use in acute ischaemia by avoiding or reducing the delayed tissue oxygenation associated with reconstruction[29,30]. Further studies are required to assess these potential benefits in clinical practice. Unless the patient is known to suffer from severe chronic obstructive airways disease, 40 per cent oxygen administration is not a hazard. As a precaution a capillary or arterial blood gas estimation can be performed to exclude chronic carbon dioxide retention.

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Short note

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New radionucleotide method of visualizing subclavian vein occlusion following temporary venous access

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Subclavian vein catheterization is an increasingly popular access route for nutrition, chemotherapy and haemodialysis[1,2]. In a recent national survey 83 per cent of renal units favoured subclavian vein cannulation as the method of access in acute renal failure or in chronic renal failure for patients awaiting permanent access[1]. Subclavian vein stenosis and thrombosis are unfortunately now recognized as serious long-term complications of subclavian vein cannulation[2,3]. Systematic radiological screening has been performed in some studies, which report the incidence of complete or partial vessel occlusion as ranging from 19 to 50 per cent. Even an occult stenosis may become clinically obvious, with the formation of arm oedema and a collateral circulation, when an arteriovenous fistula is created on the same side for haemodialysis[4]. Surgical venous reconstruction, streptokinase therapy, balloon angioplasty and ultimately ablation of the fistula by ligation may be necessary to relieve this complication[4,5]. Hence there is a need to image the subclavian vein. Classically this is achieved by radiographic venography, but radioisotope venography is quicker and cheaper, and has been used in the upper limbs when there was clinical evidence of venous occlusion[6,7]. Ultrasound imaging, especially duplex imaging with Doppler, computed tomography and digital subtraction angiography have also been described, but are relatively costly and time consuming[8,9]. The aim of this study was to investigate subclavian vein patency in patients previously treated by temporary venous cannulation for haemodialysis and to compare the results of radiographic venography with those of radioisotope imaging using technetium-99m pertechnetate.

Patients and methods

Forty combined investigations were performed on 20 patients suffering from end-stage renal failure. There were 15 men and 5 women aged 20–70 years (mean 58·6 years). All patients had previously required temporary subclavian vein catheterization for haemodialysis on one or both sides and some several times (median number of catheters per patient 1, range 1–6). Cannulae were inserted on the right side alone in 12 patients, on the left alone in one, and on both sides in seven. The right side was most commonly used for first catheterization as this is generally believed to be a technically easier site for insertion. In each case the cannula used was a double lumen Quinton–Mahurkar® (Quinton Company Ltd., Seattle, USA). As a result of subclavian vein cannulation, four patients had previously experienced complications which had resolved at the time of the study: one patient developed a pneumothorax, one a transient numbness of the arm, and two had septicaemia. For each patient the total duration of temporary subclavian access was recorded. At the time of the study all patients were being treated by continuous ambulatory peritoneal dialysis and none had clinical signs or symptoms of subclavian vein stenosis.

For the radiographic venogram the patient lay supine on the X-ray table with the arm slightly abducted. Iopamidol (Niopam 300®, E. Merck Ltd., Four Marks, UK) was injected as a 25-ml bolus into a vein in the antecubital fossa using a 20-gauge Mediport® (Sherwood Medical, Tullamore, Ireland) cannula; films were taken to show the subclavian vein, and the veins were then flushed with saline. The procedure was repeated on the other side. The cannulae were left in the veins and the patient was taken to the nuclear medicine department for the radioisotope venogram. The patient lay supine on the γ camera table with the arms slightly abducted. Technetium-99m pertechnetate 80 MBq was injected as a rapid bolus into the veins of both arms simultaneously. A sequence of images was acquired for 20 s, and later they were processed and displayed on film. The radiographic and radioisotopic venograms were reported independently by an experienced radiologist without knowledge of previous catheterization details of the patients.

Results

The radiographic and radioisotopic venograms were reported as being normal, occluded or flowing slowly through the subclavian vein. Examples of an abnormal radiographic and

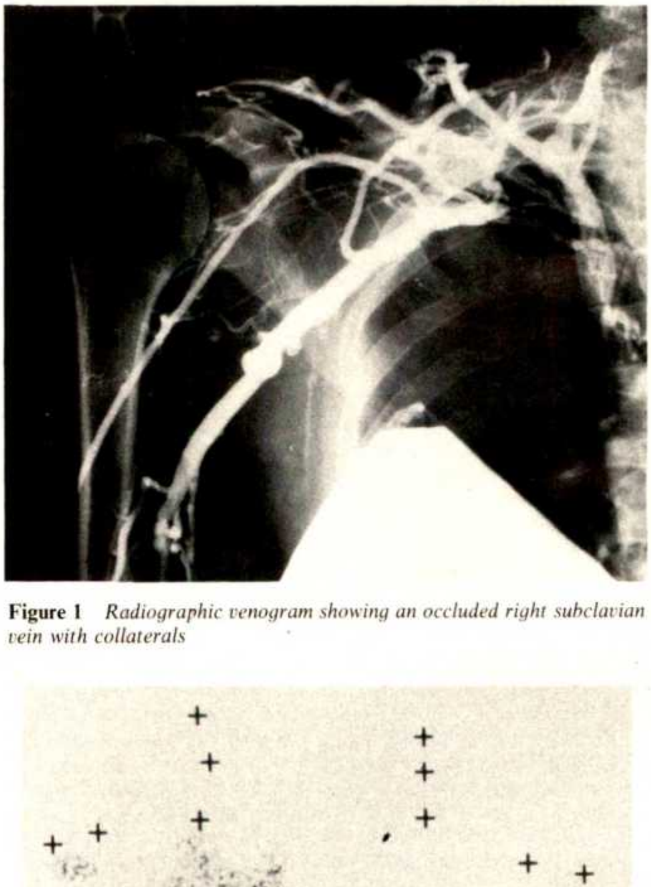

Figure 1 *Radiographic venogram showing an occluded right subclavian vein with collaterals*

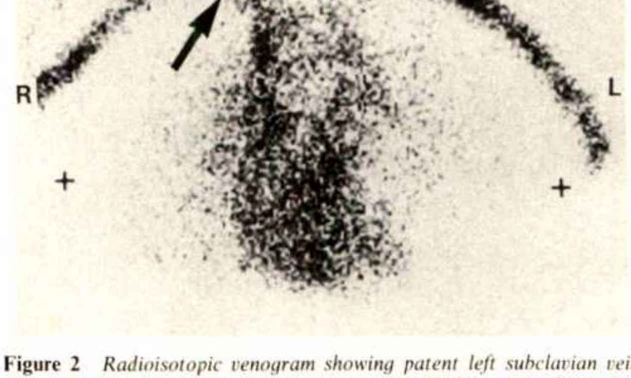

Figure 2 *Radioisotopic venogram showing patent left subclavian vein and occluded right subclavian vein (arrowed) with filling of collaterals*

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radioisotopic venogram are shown in *Figures 1* and *2*. Of the 40 scans performed 37 (92 per cent) were reported in agreement. Three occlusions were seen by both methods and represented 11 per cent of 27 subclavian veins previously cannulated. The investigations also agreed in showing slow flow in the subclavian vein of two patients, although the significance of this is uncertain. Slow flow was seen once on a radioisotope venogram but not on the corresponding radiographic venogram and once radiographically but not on the isotope venogram. A subclavian vein filling defect was seen on one radiograph and again its significance is uncertain as all patients were asymptomatic. Occluded subclavian veins occurred in three of the seven patients (43 per cent) who had received multiple bilateral subclavian vein catheterization. One patient had previously had four cannulae inserted in the vein that became occluded, and the other two patients had each had two cannulae in their occluded vein. Most patients (55 per cent) had single vessel cannulation; six had two or more cannulae *in situ* without apparent damage to their subclavian veins. Although two patients with subclavian vein occlusion had been using temporary access for up to 14 weeks (compared with a median of 4·5 weeks, range 1–41), there were insufficient data to comment on a relationship between venous occlusion and duration of cannulation.

There were two apparent delayed reactions to radiographic contrast, beginning respectively 6 and 16 h after venography. Both patients had an acute painful polyarthropathy with nausea and vomiting. Both were treated with non-steroidal anti-inflammatory drugs and made a full recovery. The first patient had had no previous joint problems. The second patient had a history of rheumatoid arthritis, but had been symptom-free for the previous year.

Discussion

In this study the radioisotopic venography proved 100 per cent accurate in the diagnosis of occult venous occlusions when compared with conventional radiographic venography. The relatively low incidence of subclavian vein occlusion may be attributable to operator skill in catheter placement and the preferential use of the right side. Although there were clear associations between the occurrence of venous occlusion and previous multiple or prolonged cannulations, these criteria are far from being diagnostic. Subclavian vein occlusion has been reported after a single short-term venous cannulation[3]. Aetiological factors in the development of vascular stenosis are believed to be prolonged contact between catheter tip and vessel wall, resulting in intimal damage, and the oscillation of the catheter during dialysis. To reduce the risk of proximal venous occlusion in a limb required for an arteriovenous access procedure, temporary venous access should be kept to a minimum and permanent procedures planned in advance of need. When acute access is required, the use of the dominant arm (normally the right) leaves the non-dominant arm available for subsequent arteriovenous fistula formation. The increased use of jugular venous access may further reduce the likelihood of proximal venous occlusion[10]. However, where it has been necessary to cannulate both arms or when the forearm veins are only suitable for fistula formation on a previously cannulated side, the simple preoperative radioisotope method described for visualizing the subclavian veins is likely to be of considerable value. There are no known reactions to technetium-99m pertechnetate. Although iopamidol, the radiographic contrast medium, is suspected of being the cause of the mild reactions, it is a very safe non-ionic low osmolar contrast medium. Contrast sensitivity of any sort is rare. Although early reactions have occurred in renal failure patients[3], there seems to be no record of similar delayed reactions. Iopamidol is normally excreted rapidly via the kidneys, but this may be delayed in patients on continuous ambulatory peritoneal dialysis.

Radioisotope subclavian venography has been found to be a quick, cheap, safe and reliable method of assessing subclavian vein patency in patents with renal failure.

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Differential effects of low-dose tissue plasminogen activator and streptokinase on platelet aggregation

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Despite increasing success with low-dose intra-arterial thrombolysis, early rethrombosis still occurs. Platelet aggregation is thought to play a major part in this process. We have therefore investigated the effects of recombinant tissue plasminogen activator (rt-PA) and streptokinase on platelet function at doses currently used for peripheral arterial thrombolysis. Platelet-rich plasma was stirred at 37°C, with either streptokinase (100, 300 or 1000 units ml^{-1}) or rt-PA (10 (T10), 30 (T30) and 100 (T100) mg l^{-1}), with immediate addition of an agonist for platelet aggregation (thrombin, collagen, adenosine diphosphate (ADP) or adrenaline) at a predetermined threshold dose. Significant inhibition of collagen-induced and adrenaline-induced platelet aggregation was produced with rt-PA at all doses used ($P<0{\cdot}05$). With adrenaline as the agonist, T100 produced disaggregation to a mean(s.d.) level of 26 (11) per cent. Thrombin-stimulated platelet aggregation was significantly reduced by T100 ($P<0{\cdot}001$) and T30 ($P<0{\cdot}01$) only, disaggregation being dose-dependent and complete with T100. Using ADP as the agonist, T100 produced a significant reduction in maximum platelet aggregation ($P<0{\cdot}01$), and disaggregation was achieved to a mean(s.d.) level of 48(13) per cent. Streptokinase did not produce any significant changes in any parameter of aggregation.

Keywords: Platelet aggregation, fibrinolytic agents, thrombolysis

Recombinant tissue plasminogen activator (rt-PA) has a high fibrinolytic activity[1,2] associated with a short half-life of <5 min[3,4]. It is relatively fibrin specific, activates fibrin-bound plasminogen to form plasmin, and does not significantly activate circulating plasminogen[5,6]. Experience with this agent for the treatment of peripheral arterial thrombosis is still limited[7–10] compared with that of low-dose streptokinase[11–19]. However, rethrombosis remains a problem with both agents; exposed endothelial collagen at the site of the thrombus causing procoagulant effects on the thrombus surface itself[20], residual thrombus[21–23], and direct activation of platelets and coagulation factors[24–27] may all play an important part. In coronary thrombolysis, rethrombosis rates of up to 45 per cent have been reported[28,29] Inadequate inflow and/or inadequate outflow cannot always be blamed and platelets are undoubtedly important in the pathogenesis of rethrombosis[30]. In coronary thrombolysis, the combination of streptokinase and aspirin has now been shown to be superior, in terms of the risk of mortality, to the use of either agent alone[31]. As yet there are no such similar studies in peripheral arterial thrombolysis. In peripheral limb arteries the volume and length of the occluding thrombus is many times greater than that in coronary thrombosis. The thrombi tend to be older and, therefore, more mature with greater cross-linking. Consequently thrombolysis takes longer. If there are significant differences in the effects of different thrombolytic agents on platelet function, this may be of considerable importance in determining the duration of lysis, the incidence of rethrombosis and the potential therapeutic benefit of concurrent administration of thrombolytic and antiplatelet agents.

We have therefore determined the effect of rt-PA and streptokinase on platelet aggregation Doses of rt-PA and streptokinase used in the experiments were based on the equivalent maximal concentration of each agent used in this centre for peripheral arterial thrombolysis

Method

Using no or minimal tourniquet time, 80 ml of blood were obtained from each of three healthy male volunteers Blood was collected into 0·109 M trisodium citrate at a ratio of 9.1. All samples were then centrifuged at 500*g* for 10 min. The supernatant platelet-rich plasma was pipetted off and platelet counts performed on a Coulter S Plus IV cell counter (Coulter Electronics Ltd., Luton, UK). The samples were centrifuged again at 2000*g* for 10 min to obtain platelet poor plasma. The platelet-rich plasma was diluted with platelet-poor plasma to a platelet count of 250×10^{9} ml^{-1}.

Threshold values for each of four agonists: thrombin (Diagnostic Reagents Ltd., Oxon, UK), collagen (Hormon-Chemie, Munich, GDR), adenosine diphosphate (ADP) and adrenaline (Sigma Chemical Company Ltd , Dorset, UK), were determined for each subject.

Plasma with a platelet count of 250×10^{9}/ml was stirred at 37°C with either saline or rt-PA (Boehringer Ingelheim, Bracknell, Berkshire, UK) at final concentrations of 10 (T10), 30 (T30) and 100 (T100) mg l^{-1}, with immediate addition of an agonist at the appropriate threshold value The same protocol was used for streptokinase (Streptase, Hoechst UK Ltd , Hounslow, UK), which was added to achieve final concentrations of 100 (S100), 300 (S300) and 1000 (S1000) units ml^{-1}. A Chronolog 440 dual channel aggrometer (Coulter Electronics Ltd., Harpenden, UK) was used at 37°C with the chart recorders set at 0·5 mm s^{-1}. Aggregation was measured from the change in light absorbance, represented in millimetres on the chart recorder. The rate of aggregation was calculated as half maximal aggregation (in millimetres) divided by the time taken to achieve half maximal aggregation (in seconds). After the lowest optical density had been reached, disaggregation was measured as the maximal increase in optical density and expressed as a percentage of the lowest optical density reached. In the case of curves that were non-reversible, maximal aggregation was taken as the aggregation present at 3 min (ADP, thrombin) or 4 min (collagen, adrenaline) after starting the experiment. The response to threshold doses was measured before and after each set of rt-PA or streptokinase concentrations was tested, and all experiments were performed at least in triplicate on prepared plasma from each of the three volunteers. Results are expressed as mean(s.d.). All statistics were performed using the Mann–Whitney *U* test.

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Table 1 *Effects of recombinant tissue plasminogen activator at final concentrations of 10 (T10), 30 (T30) and 100 (T100) mg l^{-1} on platelet aggregation*

Agonist	Control	Final concentration of rt-PA (mg l^{-1}) T10	T30	T100
Collagen				
Rate of aggregation (mm s^{-1})	0·6(0·2)	0·5(0·1)	0·5(0·1)	0·3(0·1)*
Maximal aggregation	107·9(4·9)	100·7(9·3)*	101·1(6·9)*	68·7(17·2)†
Adrenaline				
Rate of aggregation (mm s^{-1})	0·7(0·2)	0·7(0·2)	0·6(0·2)	0·5(0·1)
Maximal aggregation	97·5(4·9)	73·1(21·5)*	58·0(26·7)*	39·2(8·5)†
Thrombin				
Rate of aggregation (mm s^{-1})	0·8(0·4)	1·0(0·2)	0·8(0·3)	0·5(0·2)*
Maximal aggregation	85·2(14·9)	86·4(20·2)	32·7(11·9)†	26·3(10·3)‡
ADP				
Rate of aggregation (mm s^{-1})	1·1(0·2)	1·0(0·3)	1·0(0·2)	0·9(0·2)*
Maximal aggregation	76·6(9·7)	75·4(5·8)	72·4(9·3)	60·4(6·5)†

Results are given as mean(s.d.), * $P<0{\cdot}05$, † $P<0{\cdot}01$; ‡ $P<0{\cdot}001$, rt-PA, recombinant tissue plasminogen activator

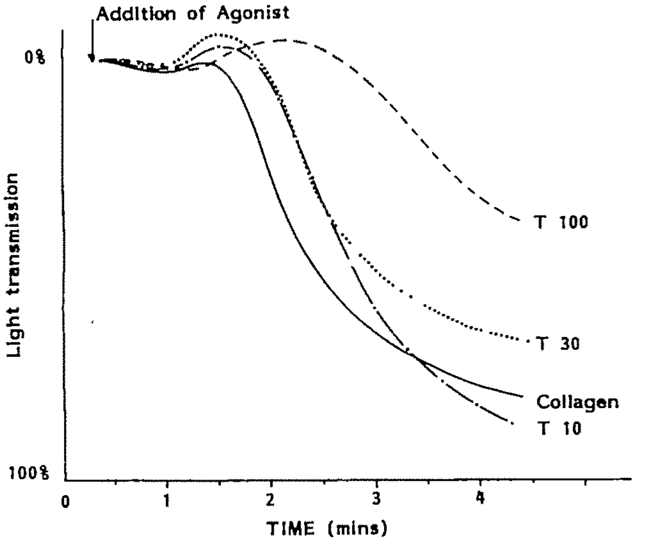

Figure 1 *Example of dose-dependent inhibition of platelet aggregation by recombinant tissue plasminogen activator following addition of collagen (1 mg l^{-1} final concentration)*

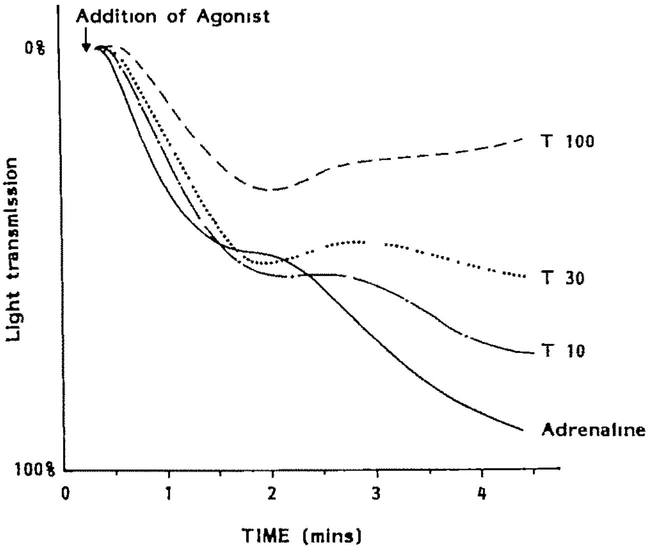

Figure 2 *Example of dose-dependent inhibition of platelet aggregation by recombinant tissue plasminogen activator (rt-PA) following addition of adrenaline (5 μmol l^{-1} final concentration) Marked disaggregation was also seen following addition of 100 mg l^{-1} rt-PA (T100)*

Results

Tissue plasminogen activator

The effects of rt-PA on platelet aggregation are described in *Table 1*.

Collagen. A single experimental example is shown in *Figure 1*. Overall, rt-PA produced significant inhibition of the maximum extent of platelet aggregation induced by collagen at all doses used ($P<0{\cdot}05$ for T10 and T30, $P<0{\cdot}01$ for T100). The rate of aggregation was also significantly reduced by T100 ($P<0{\cdot}05$). No disaggregation occurred in either the presence or the absence of rt-PA.

Adrenaline An experimental example is shown in *Figure 2*. Overall, adrenaline-induced platelet aggregation was significantly inhibited ($P<0{\cdot}05$ for T10 and T30, $P<0{\cdot}01$ for T100). At a final dose of 100 mg l^{-1}, rt-PA produced significant disaggregation to a mean level of 26(11) per cent ($P<0{\cdot}01$).

Thrombin. An experimental example is shown in *Figure 3*. Overall, thrombin-stimulated platelet aggregation was significantly reduced by T100 ($P<0{\cdot}01$) and T30 ($P<0{\cdot}01$) only The rate of aggregation was also significantly reduced by T100 ($P<0{\cdot}05$) Disaggregation was dose-dependent with a mean level of 49(20) per cent with T30 ($P<0{\cdot}001$) and 146(34) per cent with T100 ($P<0{\cdot}001$).

Adenosine diphosphate An experimental example is shown in *Figure 4*. Overall, T100 produced a significant reduction in the rate ($P<0{\cdot}05$) and maximum platelet aggregation ($P<0{\cdot}01$) following addition of ADP. Disaggregation was consistently achieved only with T100, with a mean level of 48(13) per cent ($P<0{\cdot}001$).

Streptokinase

Streptokinase did not produce inhibition of either the rate of aggregation or the extent of aggregation, following the use of any of the four agonists in an analogous protocol

Discussion

Our results show that rt-PA can cause significant inhibition of platelet aggregation *in vitro*. The doses used in this study are based on the theoretical concentration of rt-PA or streptokinase delivered to an occluding thrombus using our standard protocol for local low-dose intra-arterial thrombolysis (33 mg l^{-1} rt-PA, 333 units ml^{-1} streptokinase).

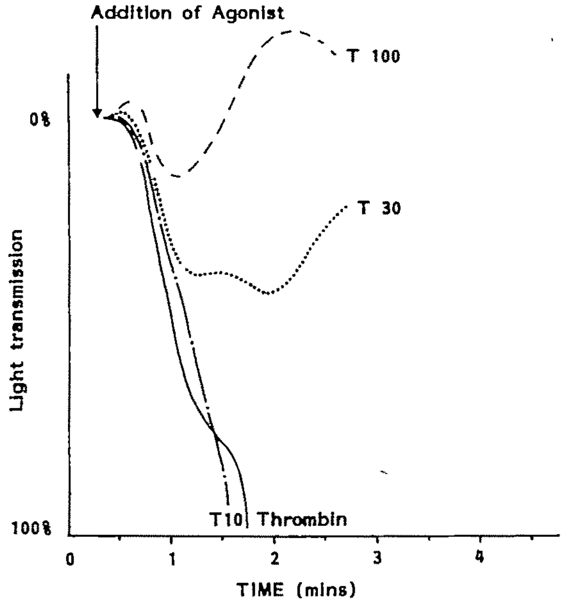

Figure 3 *Example of significant inhibition of platelet aggregation by 30 (T30) and 100 (T100) mg l^{-1} recombinant tissue plasminogen activator (rt-PA) following addition of thrombin (0·3 units final concentration). Disaggregation was seen following addition of 30 and 100 mg l^{-1} rt-PA*

A dose-dependent inhibition of collagen-induced platelet aggregation was produced by rt-PA, which was highly significant at the T100 concentration ($P<0{\cdot}01$). The rate of aggregation was also significantly reduced with rt-PA at this concentration ($P<0{\cdot}05$). No disaggregation was seen using the doses of rt-PA studied. In contrast, Loscalzo and Vaughan[32] found that collagen-induced platelet aggregation was resistant to rt-PA. This is because they were primarily studying the effects of rt-PA on disaggregation rather than inhibition of aggregation. In their protocol, rt-PA was added 1 min after the addition of agonist at a point where marked platelet aggregation had already occurred. Although our results demonstrate that rt-PA can significantly inhibit platelet aggregation induced by collagen, we agree that it cannot achieve disaggregation. The explanation of this phenomenon may be that platelets aggregate in response to collagen via fibrinogen-independent, as well as fibrinogen-dependent, mechanisms[33]. Platelets adhering to collagen release ADP, which promotes irreversible platelet aggregation.

Adrenaline-induced platelet aggregation was also significantly inhibited by all doses of rt-PA used. At the highest dose, disaggregation was seen to a mean level of 26(11) per cent.

Dose-dependent inhibition of platelet aggregation induced by thrombin was seen. rt-PA also produced dose-dependent disaggregation to a mean level of 146(34) per cent at the T100 concentration, suggesting that the final light transmission was actually lower than in the original sample. This may be due to disaggregation of previously formed platelet microaggregates, but this is only an hypothesis. These results verify the findings in earlier work[32]. The method of adding thrombin to platelet-rich plasma is not often used because of the difficulty in interpretation of the consequent increase in light transmission. This may be due to a combination of platelet aggregation and coagulation. However, using the same protocol with streptokinase, we did not see any significant effect on the rate or extent of aggregation using clinically equivalent doses, and so the effects seen can be attributed to rt-PA alone.

Only the highest concentration of rt-PA produced significant inhibition of platelet aggregation induced by ADP ($P<0{\cdot}01$). Loscalzo and Vaughan[32] found that rt-PA produced disaggregation when added to a suspension of ADP-aggregated platelets. This effect was dependent on dose and time. The earlier the rt-PA was added, the faster the rate of disaggregation and the greater its extent. The effect was inhibited by incubation of the platelet-rich plasma with α_2-antiplasmin before adding ADP. They concluded that disaggregation was the result of the proteolytic effect of plasmin and not the result of the amidolytic effect of rt-PA itself. Aspirin potentiated the effect on the rate of disaggregation over a wide range of rt-PA concentrations. Some disaggregation was seen[28] at concentrations of rt-PA as low as 5 mg l^{-1}. Whether local concentrations of rt-PA secreted by the vascular endothelium reach these levels is not known. It is unclear why rt-PA does not have such marked effects in our own study. In contrast, using New Zealand White rabbits, Ohlstein *et al.*[34] demonstrated that rt-PA at doses of 10 and 30 μg kg^{-1} min^{-1} produced *ex vivo* platelet hyperaggregability when collagen, arachidonic acid or ADP was used as the aggregating agent. These effects were apparently more pronounced at lower and subthreshold doses of collagen. Platelet counts were significantly decreased (by 16–22 per cent compared with control values). Streptokinase was also used in the same system: after a bolus dose of 40 000 units, a maintenance dose of 4000 units min^{-1} for 15 min was used. A similar platelet hyperaggregability was observed. The authors concluded that, following addition of rt-PA, platelet hyperaggregability was more common but of a shorter duration than following addition of streptokinase. The platelet hyperaggregation and thrombocytopenia observed in this study after systemic administration of rt-PA or streptokinase may be due to enhanced plasmin activity. Plasmin has a biphasic response, causing inhibition of platelet aggregation[35] and thromboxane B_2 production at low doses, but acting as a platelet agonist[36,37] at high doses. The doses used, 10 and 30 μg^{-1} kg^{-1} min^{-1}, are respectively equivalent to 42 and 126 mg h^{-1} for a 70 kg man. These are many orders of magnitude higher than those used in our own clinical study in humans and so direct comparison is not possible.

Although we have shown significant inhibition of platelet aggregation by rt-PA, we have shown neither inhibition nor enhancement of aggregation or of disaggregation by streptokinase. However, Fitzgerald *et al.*[25,38] have recently reported marked platelet activation following coronary thrombolysis with streptokinase. With additional *in vitro* tests they showed that the proaggregating effect was dose-dependent and seen over a range of 300–3000 units ml^{-1} with the maximum effect at 1883(440) units ml^{-1}. The mechanism of action is thought to involve plasminogen because, by passing citrated platelet-

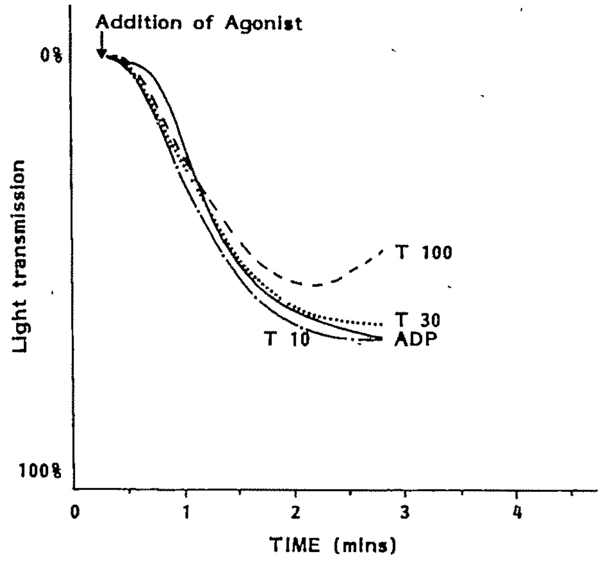

Figure 4 *Example showing that only 100 mg l^{-1} recombinant tissue plasminogen activator (T100) produced significant inhibition of maximal platelet aggregation and of the rate of aggregation following addition of adenosine diphosphate (2 µmol l^{-1} final concentration)*

rich plasma over a lysine–sepharose column to remove plasminogen, the proaggregatory effect of streptokinase (but not ADP) was prevented. The effect was subsequently restored by the addition of exogenous plasminogen. In contrast, after rt-PA therapy for myocardial infarction, platelet activity remains relatively unchanged[39]. Although our own study failed to demonstrate an enhancement of ADP-induced aggregation by streptokinase, we used a threshold dose of ADP, which was defined as the lowest concentration of ADP required to achieve progressive aggregation throughout the study period. In order to demonstrate similar enhancement of aggregation by streptokinase, we would need to repeat these experiments with lower doses of ADP to achieve minimal, reversible aggregation like Fitzgerald *et al.*[38]. It is also known that streptokinase can initiate specific antibody-mediated platelet aggregation *in vitro* and this may be associated with clot propagation and thromboembolism *in vivo*[40,41]. The extent of platelet aggregation induced by streptokinase correlates with the titre of antistreptococcal antibodies[42], which are present in up to 10 per cent of patients[43]. Antistreptococcal antibodies were not measured in our subjects; however, any potential augmentation of aggregation was not apparent at the doses of agonist used.

Various animal studies have also demonstrated that platelet activation does modify the response to streptokinase and other fibrinolytic agents[44,45]. Platelet aggregation is accompanied by platelet release reactions, which may have adverse physiological effects. The increase in biosynthesis of thromboxane A_2, a potent platelet agonist and vasoconstrictor[46], in Fitzgerald's study far exceeded the level in patients with unstable angina[47], in whom there is a beneficial effect of aspirin[48,49].

Various theories have been proposed to explain the platelet effects. Fibrinogenolysis will impair ADP-induced platelet aggregation as fibrinogen is a necessary cofactor[50]. Further impairment of aggregation and adhesion[51] is seen as a consequence of cleavage of glycoproteins Ib and IIb/IIIa (receptors for von Willebrand factor and fibrinogen respecspectively[52,53]), following activation of platelet-bound plasminogen[54]. Plasmin-induced cleavage of thrombospondin, fibronectin and fibrin can disrupt the matrix and result in platelet disaggregation[32]. This mechanism is enhanced by fibrinolytic agents, resulting in lysis of the fibrin framework that holds the platelets together.

The clinical importance of these enhanced platelet effects is uncertain. Groups of patients with thrombosis or at risk of thrombosis appear to have increased platelet adhesiveness[55], increased spontaneous aggregation[56], a reduced threshold to a range of agonists[57], and increased platelet release reactions[58]. However, although the mean values of all these parameters achieve significance for the groups as a whole, there is sufficient overlap with control populations to make their use in individual cases clinically unreliable. Nevertheless, an agent with platelet inhibitory rather than proaggregatory characteristics would appear highly desirable.

The concurrent use of an antiplatelet agent and a fibrinolytic agent may cause concern because of the potential bleeding complications. However, in the ISIS-2 study[31], although the combination of aspirin and streptokinase was associated with a 0·7 per cent increase in frequency of minor bleeds, no increase in major bleeds was noted and there was a 0·5 per cent reduction in the risk of stroke.

In our study rt-PA has been shown to have important dose-dependent inhibitory effects on all four platelet aggregation agonists assessed. Furthermore, using the same protocol with streptokinase, no significant inhibition of any parameter for any agonist is seen. These effects may help to explain the more rapid lysis seen with rt-PA in peripheral arterial thrombolysis compared with streptokinase[10], and may also help to reduce early rethrombosis. Concurrent therapy with antiplatelet agents may confer a greater effect with streptokinase than with rt-PA. Further *ex vivo* assessment of platelet behaviour using patients receiving peripheral arterial thrombolysis is required to substantiate these findings.

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Subclavian aneurysm: a presentation of Takayasu's arteritis

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Takayasu's disease is a non-specific arteritis affecting the aorta and its major branches. It generally affects young women and is uncommon outside the Orient. We report an unusual case of this disease, presenting with an isolated aneurysm.

Case report

A 19-year-old woman presented with a painless lump in the right supraclavicular region and occasional tingling in the right hand. The lump was first noticed 6 months previously and had recently enlarged. There was no history of preceeding trauma. Her general health was excellent. She had been treated for pulmonary tuberculosis 11 years previously and at regular follow-up there were no signs of recurrent disease.

On examination she was apyrexial and normotensive. There was a diffuse 3 cm pulsatile swelling (with an associated loud bruit) in the right supraclavicular region, just lateral to sternomastoid and filling the supraclavicular fossa. Neurological examination of the right hand and arm was normal. There was no evidence of embolization.

A chest X-ray showed no signs of active tuberculosis. Haemoglobin, blood film, urea and electrolytes were normal. The erythrocyte sedimentation rate was not measured. Intravenous digital subtraction angiography demonstrated a saccular aneurysm arising from the proximal portion of the right subclavian artery (*Figure 1*). The aortic arch and its remaining branches except the right vertebral artery (which was not visualized) were normal. The aneurysm appeared much smaller than the clinical mass suggesting the presence of thrombus within it.

At operation, via transverse subclavicular and supraclavicular approaches, the aneurysm was exposed and dissected free of the phrenic nerve and brachial plexus. A 6 mm woven Dacron® (du Pont) graft was anastomosed end-to-side to the right common carotid artery. The subclavian artery was then ligated proximal to the aneurysm. The distal portion of the graft was anastomosed end-to-end to the axillary artery. The aneurysm was opened and feeding vessels were under-run from within the sac. Mural thrombus, aneurysm wall and adjacent macroscopically normal arterial wall were sent for culture and histological examination. The patient recovered uneventfully, and at follow-up 1 year later she was symptom-free and the graft was functioning well. Subsequent measurements of erythrocyte sedimentation rate were normal.

There was no evidence of tuberculosis on culture or histological examination. Sections of aneurysm wall showed lymphocytic and plasma-cell infiltration of the adventitia with a neutrophil vasculitis of the vasa vasorum. There was marked irregular loss of the elastic laminae and medial necrosis. No evidence of granulomata or Langhans' giant cells was found. Sections from the adjacent arterial wall were normal. From clinical and histological findings the pathologist diagnosed Takayasu's arteritis.

Discussion

The differential diagnosis in this case included atheroma, mycotic aneurysm, giant cell arteritis and Takayasu's disease. There was no evidence on enquiry or physical examination of significant atheromatous disease. Tuberculosis has long been recognized as an infrequent cause of arterial aneurysms, mainly affecting the aorta. Occasional cases of isolated subclavian aneurysm have been reported[1] associated with recently active pulmonary tuberculosis. In this country, tuberculosis is still quite common, while Takayasu's arteritis is rare. Most patients with Takayasu's are young Oriental females and in more than a quarter of cases there is a past history of tuberculosis[2]. General malaise, significant cardiac and pulmonary symptoms are found in about two-thirds of patients and these factors influence the natural history and prognosis[3]. Clinical differentiation between Takayasu's and giant cell arteritis may be difficult when there is an isolated aneurysm without occlusion. Vinijchaikul[4] reported eight cases of Takayasu's of which one presented in this way, but the most common presentation is of vessel occlusion.

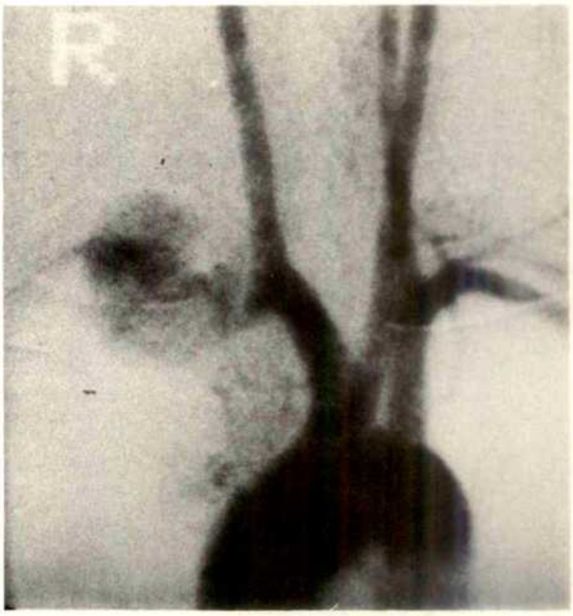

Figure 1 *Intravenous digital subtraction angiography of the aortic arch showing the right subclavian aneurysm*

The histological findings in this case are in keeping with those 'acute-stage lesions' described by Lagneau *et al.*[5], with a predominance of cellular infiltration, disruption of the external elastic lamina but preservation of the internal media. Although corticosteroids can produce dramatic symptomatic relief and may be of benefit in more advanced disease, there is little evidence to support their use in early isolated Takayasu's arteritis. The mortality rate within 2 years in recent reported series[2,3,4] varied between 7 and 16 per cent. Early treatment of the inflammatory process appeared to improve prognosis. Careful follow-up is the mainstay of treatment as surgery or corticosteroid therapy may be required to treat further manifestations of Takayasu's arteritis. With careful follow-up the prognosis in otherwise asymptomatic patients is excellent.

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Surgical workshop

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Electrocardiographic guided placement of central venous catheters

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Central venous catheterization is commonly performed for both venous access and central venous pressure monitoring. Central venous access may be required for the administration of chemotherapeutic agents, parenteral nutrition, haemodialysis, plasmapheresis and plasma exchange. The large number of available devices for accessing the central venous circulation include silastic and polyethylene single and multilumen catheters, double lumen haemodialysis catheters, and venous access discs for subcutaneous implantation[1–4].

Standard placement techniques, whether by venous cutdown or percutaneous venepuncture, depend on radiological confirmation of catheter tip position by either fluoroscopy or static X-ray. While both methods are accurate and may produce hard copy documentation of catheter tip position, they are cumbersome, requiring specialized equipment and personnel.

We describe a technique for central venous catheterization based on electrocardiographic principles, first utilized for the placement of ventriculoatrial shunts[5,6]. This method uses the catheter, filled with a conducting medium, as an exploring electrode; the catheter tip position is judged by easily observable and reproducible P wave changes on an electrocardiographic monitor. The technique is simple and easily mastered, requires equipment routinely found in all operating theatres, and may be adapted to clinical settings outside the operating theatre. When performed properly, the method is accurate and reliable.

Surgical technique

Einthoven's triangle conceptualizes the body as a volume conductor, and describes the surface representation of cardiac electrical activity during the depolarization–repolarization process. Signal polarity depends on the orientation of the sensing electrodes and the vector of the cardiac electrical events[7]. When a transvenous probe is used as the negative lead, and the left leg position as the positive lead, positive deflections are encountered for the P waves, T waves, and QRS complexes when the heart is approached transvenously via the superior vena cava. *Figure 1* illustrates the changes in P wave configuration when a transvenous electrode as described passes through the superior vena cava, right atrium, and right ventricle.

This method utilizes the central venous catheter as the exploring transvenous electrode. Electrocardiographic leads are placed in the standard left and right upper and lower extremity positions and connected to an electrocardiographic oscilloscope. After the vein (the internal jugular, external jugular or cephalic) is exposed and controlled, the catheter tubing is tunnelled from the chest wall or subcutaneous pouch into the neck wound. The line is flushed with 0·9 per cent saline, and threaded through the venotomy for a distance of 4–6 cm. An 18 gauge needle is placed at the end of the catheter tubing, and the line is filled with 3 per cent saline. An insulated connecting wire (Medical

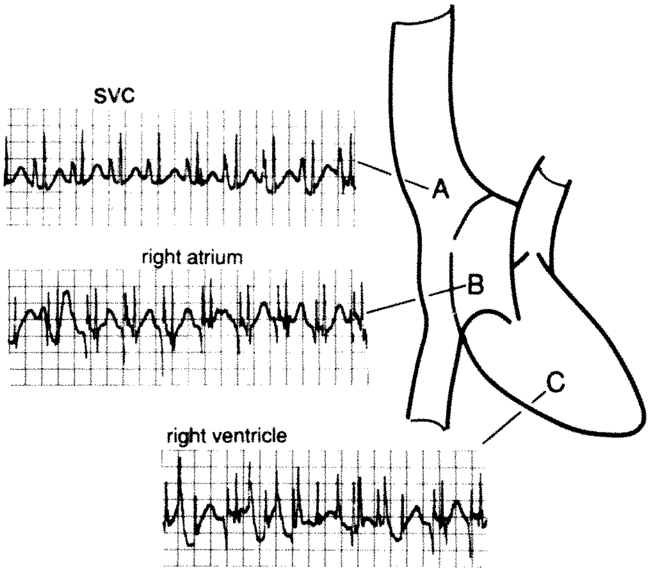

Figure 1 *P wave changes observed in Lead III as the catheter passes through the superior vena cava into the right atrium and right ventricle. A, Superior vena cava (SVC); B, right atrium; C, right ventricle*

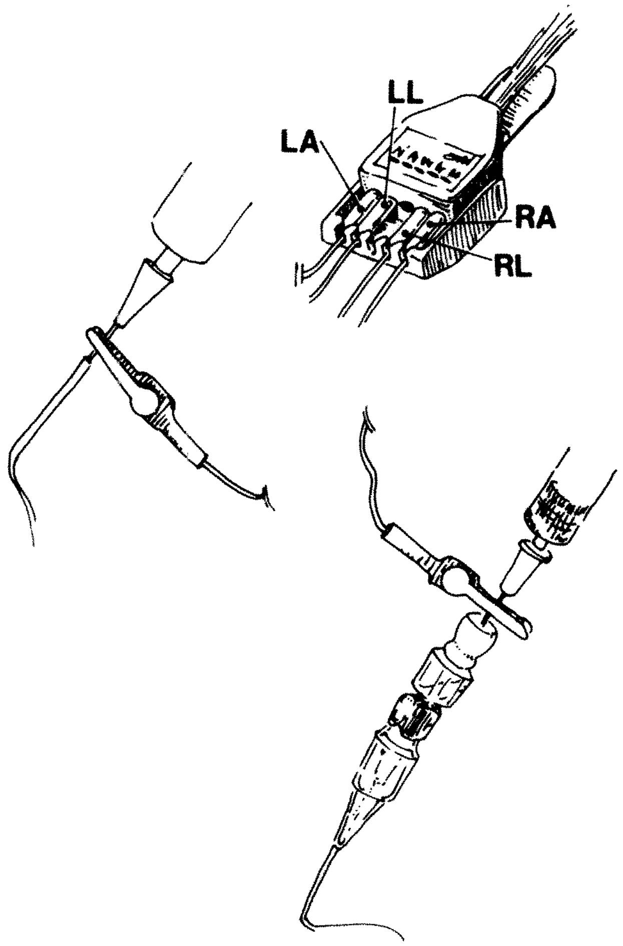

Figure 2 *Connecting cord. The alligator clip attaches to an 18 gauge needle, and the adaptor at the other end attaches to the left arm input station of the oscilloscope. Note that a blunt tipped 18 gauge needle is used when interfacing with venous access disc catheter tubing. A standard 18 gauge needle is passed through a rubber hub adaptor when silastic or polyethylene lines are utilized. LA, left arm; LL, left leg; RA, right arm; RL, right leg*

Engineering Department, Hospital for Sick Children, Toronto, Ontario, Canada) is attached to the metallic portion of the 18 gauge needle with an 'alligator' clip, and an appropriate electrical connector attaches the other end of the wire to the left arm input station of the electrocardiographic oscilloscope (*Figure 2*). The tracing is then observed on standard Lead III, noting the P wave configurational changes as the line is repositioned. The catheter is advanced slowly and, as the right atrium is entered, biphasic P waves are noted (*Figure 1*, B). The central venous line is withdrawn carefully. As the tip of the catheter moves from the right atrium into the superior vena cava, the P waves become monophasic, with spiked peaks (*Figure 1*, A). Further withdrawal dampens the P waves toward normal. The point at which the P wave first normalizes is the proper position of the catheter tip.

If no P wave changes are noted after a reasonable length of catheter has been advanced through the venotomy, the catheter has not entered the superior vena cava. The catheter is withdrawn back to the venotomy site, and further attempts to enter the central circulation are made. If P wave changes cannot be obtained after several efforts, a different venous route is chosen. Once proper placement is achieved, the catheter is secured and the neck incision closed.

Discussion

Experience of this technique of central venous catheterization has been obtained in over 400 neonates, infants and children, and in a prospective study in 50 consecutive patients the accuracy of electrocardiographic guided placement by subsequent chest X-ray[8] has been confirmed. Correct catheter position within the central venous circulation is invariably achieved when this method is properly executed. Conversely, the absence of P wave changes denotes improper positioning, and is a cause to abandon an unsuccessful route after multiple attempts.

While we do not routinely perform percutaneous central venous catheterization in infants and children, this technique can be easily adapted for this purpose, and a standard electrocardiograph machine may be substituted for the oscilloscope.

It has been our experience that patients with cardiac pacemakers or supraventricular dysrhythmias present a special problem, and in general, this technique cannot be used in this small group of patients. Fluoroscopic guide placement is the preferred method in this clinical setting.

We present a technique for central venous catheterization which utilizes the catheter as a probing electrode. The technique is accurate, can be easily mastered and taught to surgeons in training, uses equipment found in all operating theatres or accessible on most wards, and eliminates the need for X-ray to confirm catheter tip position.

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Complications of parotid surgery: the need for selectivity

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The morbidity rate following 112 operations on the parotid gland is reported. Facial nerve palsy (temporary, 38 per cent; permanent, 9 per cent) and Frey's syndrome (11 per cent) were common following superficial parotidectomy. For pleomorphic adenoma and malignant lesions this procedure is justified. Benign conditions, which can be diagnosed preoperatively, should be treated by more limited surgery which has a lower complication rate.

Keywords: Parotidectomy, complications

Superficial parotidectomy has become the preferred method of treating space-occupying lesions of the parotid gland over the past 25 years[1,2] We have assessed the morbidity rate associated with this procedure over a 10-year period and compared it with that following local resection in lesions diagnosed preoperatively as benign by fine needle aspiration cytology (FNAC) – a technique we have previously reported[3].

Patients and methods

The records of 112 patients who had parotid gland masses operated on at Northwick Park Hospital (1977–87) and have been followed for a minimum of 12 months were reviewed retrospectively. Of these operations, 80 were performed by one consultant surgeon (A.E.K.) and ten by an experienced registrar (E.R.T C.O.) under the same consultant's supervision. The remaining procedures were done by another consultant. The operating registers and pathology records were carefully checked to ensure that all patients who underwent parotid surgery during this 10-year period were reviewed.

In all, 90 patients were contacted; 25 have been followed for 1–3 years, 25 for 3–5 years and 40 for more than 5 years Ten patients (9 per cent) died within 2 years of operation from unrelated causes and were free of recurrence at time of death. Twelve patients (11 per cent) were lost to follow-up. The commonest operation, carried out in 86 per cent (96 patients), was excision of the mass together with a surrounding rim of normal parotid tissue, i.e. superficial parotidectomy as described by Hobsley[4]. The remaining 14 per cent (16 patients) had limited surgery, i e. enucleation or excision biopsy, and this approach was adopted on the basis of a preoperative diagnosis of a benign lesion using FNAC.

Facial nerve damage was assessed according to the Chan and Gunn modification[5] of Patey's classification[6] in which grade III is a major weakness affecting all branches, grade II is moderate weakness affecting either eye or mouth, and grade Ib is minimal weakness at the angle of the mouth.

Results

The pathological findings consisted of benign lesions (59 cases, 53 per cent), pleomorphic adenoma (46 cases, 41 per cent) and malignant tumours (seven cases, 6 per cent). The benign lesions included 20 adenolymphomas, which thus comprised 18 per cent of all the cases or about 27 per cent of the tumours. The other benign lesions included enlarged lymph nodes, granulomas, tuberculomas and cysts.

The incidence of major complications according to pathology and type of operation is shown in *Table 1*. The complication rate in patients with benign pathology was the same as in those with pleomorphic adenomas and malignant tumours, whereas no significant complications occurred after limited surgery.

Facial nerve palsy occurred in 53 patients (47 per cent) (*Table 2*). Of ten patients with permanent palsy, six had deliberate sacrifice of a branch of the nerve as it passed directly into the tumour, and in the other four the tumour was situated deep to the facial nerve. In five of these the pathology was benign.

Frey's syndrome was seen in 12 patients, all following superficial parotidectomy. Six of these were severe and the other six were socially embarrassing. Half of these patients had benign pathology.

Spillage or incomplete excision occurred in 16 cases, six following superficial parotidectomy. One recurrence occurred 30 months after superficial parotidectomy, without spillage, for a pleomorphic adenoma. Minor complications included haematoma (16 per cent), temporary fistula (2 per cent), facial paraesthesia (32 per cent), painful neuroma (6 per cent) and keloid (3 per cent).

Discussion

Superficial parotidectomy for pleomorphic adenoma[1] has reduced the recurrence rate to less than 1 per cent[7]. This operation has significant complications.

Permanent facial nerve palsy

The reported incidence of permanent facial nerve palsy varies between 0 and 17 per cent[6–12] (9 per cent in this series). It occurs after all types of operation but in this report did not follow limited procedures. It is to be expected after deliberate sacrifice of a branch passing into a tumour, although this is not always the case.

Temporary facial nerve palsy

The reported incidence varies between 11 and 82 per cent[6–12] (38 per cent here, though no cases occurred after limited surgery). Normal function usually returns within 3–6 months, but it may take up to a year. It may be caused by nerve ischaemia, fatigue from excessive stimulation, stretching or haematoma formation[5]. The effects of this complication while it lasts are as devastating as a permanent palsy, and may cause depressive illness.

Frey's syndrome

The reported incidence varies between 2 and 43 per cent[6–12] (11 per cent here), but if the starch–iodine test is carried out it is almost always present to some degree[13,14]. It is seen only after superficial parotidectomy, as confirmed in this report. Although often dismissed lightly, the extent of the social incapacity ranges from regular mopping during eating to a virtually housebound existence.

The most significant finding is the number of major complications in the 59 patients with quite innocent pathology: 8 per cent permanent palsy, 36 per cent temporary palsy and 10 per cent Frey's syndrome. All of these complications followed superficial parotidectomy (48 patients). None occurred after limited surgery. When the latter is combined with radiotherapy,

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Table 1 *Major complications*

	According to operation			According to pathology		
	Superficial parotidectomy (*n*=96)	Limited surgery (*n*=16)	Total (*n*=112)	Pleomorphic (*n*=46)	Malignant (*n*=7)	Benign (*n*=59)
Temporary facial palsy	43 (45)	0	43 (38)	19 (41)	3 (43)	21 (36)
Permanent facial palsy	10 (10)	0	10 (9)	4 (9)	1 (14)	5 (8)
Frey's syndrome	12 (12)	0	12 (11)	6 (13)	0	6 (10)

Values in parentheses are percentages

Table 2 *Incidence of facial nerve damage*

Distribution of weakness	Temporary palsy	Permanent palsy
Grade Ib	16	5
Grade II	16	4
Grade III	11	1
Total	43 (38)	10 (9)

Values in parentheses are percentages

however, permanent and temporary palsy have been reported[15,16].

Benign lesions require only enucleation. Such limited surgery does reduce complications. The selection of cases for a conservative approach requires a reliable method of preoperative diagnosis. We have previously reported the role of FNAC and computed tomography in the management of parotid swellings[3,17]. Aspiration cytology has a predictive accuracy of more than 95 per cent[3,17–22]. Many of the cases in this series were not assessed by FNAC. This has become part of our standard practice only recently, and the accuracy of FNAC cannot therefore be assessed from this study. Despite fears of tumour dissemination by this technique, no case of tumour seeding has been reported using a fine needle with a single pass technique. We do not routinely excise the needle track as it is usually difficult or impossible to identify. Careful follow-up is required to confirm that the long-term risk of implantation is negligible. In our experience aspiration cytology has provided, in every case, the distinction between benign lesions and pleomorphic adenoma.

The surgical removal of a parotid tumour should be planned on the basis of preoperative cytological diagnosis to enable surgery to be tailored appropriately and so reduce the complications of unnecessarily extensive procedures.

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Laparoscopy, ultrasound and computed tomography in cancer of the oesophagus and gastric cardia: a prospective comparison for detecting intra-abdominal metastases

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We have evaluated the sensitivity, specificity and accuracy of laparoscopy under general anaesthesia, ultrasound and computed tomography (CT) in detecting intra-abdominal metastases in 90 consecutive patients with carcinoma of the oesophagus or cardia. Metastases were histologically confirmed as hepatic in 25 patients, nodal in 35 and peritoneal in nine. All investigations had high specificity (86–100 per cent) for each type of metastasis. Laparoscopy was found to be significantly more sensitive ($P<0.01$; $P<0.02$) *and more accurate* ($P<0.01$; $P<0.01$) *than either ultrasound or CT, respectively, with regard to hepatic status. Although laparoscopy performed best with regard to nodal metastases, this reached statistical significance only when sensitivity of ultrasound was compared* ($P<0.01$)*. Neither ultrasound nor CT detected any peritoneal metastases, although laparoscopy detected eight out of nine, giving a sensitivity of 89 per cent and an accuracy of 98 per cent. There was no morbidity or mortality associated with laparoscopy, which offers a safe, reliable method of determining intra-abdominal status and may obviate the need for surgery in some patients with malignant dysphagia.*

Keywords: Carcinoma of oesophagus or cardia, intra-abdominal metastases, laparoscopy, ultrasound, computed tomography, accuracy

Squamous carcinoma of the oesophagus and adenocarcinoma of the cardia, although biologically different tumours, have a number of common features. Both are associated with distressing dysphagia, resection carries a high level of operative risk, and prognosis is poor, especially in the presence of disseminated disease. It is now possible to achieve adequate palliation of malignant dysphagia in patients with widespread disease, or who are unfit for major surgery, by a variety of non-operative methods. The accurate and reliable detection of intra-abdominal metastatic disease is therefore of considerable importance if needless surgery is to be avoided.

Hepatic metastases are usually associated with a poor prognosis, and knowledge of their presence or absence has a significant bearing on therapeutic decisions in a variety of malignant diseases. Various methods for the preoperative detection of hepatic metastases have been assessed, including biochemical tests of liver function, isotope liver scanning and, more recently, ultrasound scanning and computed tomography (CT). All of these methods have limitations and drawbacks, not least of which, particularly regarding CT, may be availability and cost. There is little information regarding the effectiveness of these non-invasive tests in detecting other intra-abdominal metastases, particularly peritoneal or nodal metastases, which may also have an influence on therapeutic options.

Laparoscopy has been evaluated in the assessment of intra-abdominal dissemination in patients with gastric[1,2], pancreatic[3], biliary[4,5] and a number of non-gastrointestinal malignancies[6–10]. There are few studies on the role of laparoscopy in the preoperative assessment of patients with dysphagia due to carcinoma of the oesophagus or cardia. A prospective, comparative evaluation of the accuracy of laparoscopy, ultrasound and CT in detecting intra-abdominal metastases in patients with carcinoma of the oesophagus and adenocarcinoma of the cardia is presented.

Patients and methods

Between February 1986 and October 1988, 90 consecutive patients with dysphagia were studied. All had biopsy-proven carcinoma of the oesphagus or cardia but patients with extensive proximal gastric cancer involving the cardia were not included. All patients underwent abdominal ultrasound using an Advanced Technology Laboratories (Washington, UK) real-time ultrasound scanner fitted with a 3·5 MHz transducer, contrast enhanced CT using an EMI model 5005 whole body scanner (EMI Ltd, Hayes, UK) and laparoscopy. Laparoscopy was carried out under general anaesthesia with intermittent positive pressure ventilation. An Olympus® (Keymed, Southend, UK) oblique viewing laparoscope was used with an Eder Insumat Insufflator® (Down Surgical Ltd., Mitcham, UK). The laparoscope was usually inserted subumbilically and when indicated a liver biopsy was obtained with a Tru-Cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) biopsy needle under direct vision. Instruments for laparoscopic manipulation and punch biopsy were not available. Each investigation was carried out by a single investigator without prior knowledge of the results of the other two investigations. However, the results of all three investigations were collated along with other pertinent data when decisions regarding individual patient management were made.

Intra-abdominal metastases were considered to be proved only when histological confirmation was obtained either by laparotomy and biopsy, or by laparoscopy and biopsy and, on occasion, by autopsy findings.

The sensitivity, specificity and accuracy of each technique was calculated using the decision matrix and formulae of McNeil and Adelstein[11]. Thus the sensitivity of each investigation is the proportion

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Table 1 *Patient details*

Number of patients	90
Age (years)	
Range	40–93
Mean	64
Male:female	55:35
Squamous carcinoma ($n=36$)	
Upper third	11
Middle third	19
Lower third	6
Adenocarcinoma ($n=54$)	
Cardia	45
Oesophagus	9

Table 2 *Histologically proved intra-abdominal metastases by site of tumour and pathology*

		Intra-abdominal metastases		
Primary lesion	n	Hepatic	Nodal	Peritoneal
Squamous carcinoma				
Upper third	11	2 (8)	–	–
Middle third	19	4 (16)	9 (26)	4 (44)
Lower third	6	2 (8)	4 (11)	–
Adenocarcinoma				
Upper third	3	–	–	–
Middle third	12	1 (4)	8 (23)	–
Lower third	39	16 (64)	14 (40)	5 (56)
Total	90	25	35	9

Values in parentheses are percentages

of positive tests in all patients with proven disease; the specificity is the proportion of negative tests in all patients proved not to have disease, and the accuracy is the ratio of correct results (true positive + true negative) to the total number of tests. The statistical difference between tests was calculated using a χ^2 test with Yates' correction.

Results

There were 55 men and 35 women aged 40–93 years with a mean(s.d.) age of 64(11·7) years. Of 36 cases of squamous carcinoma, 11 involved the upper third of the oesophagus, 19 the middle third, and six the lower third. In 54 cases of adenocarcinoma, 45 involved the cardia but were mainly in the oesophagus rather than stomach, and nine were confined to the oesophagus – three in the upper and six in the middle third (*Table 1*).

Laparotomy was performed on 65 patients, of whom 38 had resection of the primary tumour. Of the 27 patients not having resection of the tumour, 15 had Celestin® (Ambleletin Ltd., Gloucester, UK) intubation either as a planned primary procedure (eight cases) or because of failure to pass a guide-wire at attempted endoscopic intubation (seven cases). Twelve patients were found to have advanced disease at laparotomy, three of whom were managed by Atkinson intubation, eight by laser therapy and one by chemotherapy. No surgery was performed in 25 cases, either because widespread metastatic disease was proved (20 cases) or because they were considered unfit for major surgery (five cases). Twelve were managed by pulsion intubation, 11 by laser therapy and two by radiotherapy.

The number, distribution and origin of intra-abdominal metastases are presented in *Table 2*. Intra-abdominal metastases were present in 20 (51 per cent) of the 39 patients with upper or middle third lesions and in 30 (59 per cent) of the 51 patients with lower third or cardia lesions.

There was a total of 25 patients with hepatic metastases that were confirmed histologically either by laparotomy and biopsy or by laparoscopy and percutaneous biopsy under direct vision. None of these patients had hepatomegaly or abnormal liver function tests. Of these, 17 (68 per cent) were in patients with primary adenocarcinoma and eight (32 per cent) in patients with squamous carcinoma. Seven (28 per cent) occurred in association with upper or middle third lesions and 18 (72 per cent) in association with lesions of the lower third of the oesophagus or cardia.

Thirty-five patients had nodal metastases proved by laparotomy and subsequent histology. Twenty-two (63 per cent) of these were in patients with adenocarcinoma and 13 (37 per cent) in those with squamous carcinoma. Sixteen (46 per cent) nodal metastases were associated with upper or middle third lesions and 19 (54 per cent) with lower third lesions or lesions of the cardia. Nine patients had peritoneal metastases proved at laparotomy: five (56 per cent) in patients with adenocarcinoma, four (44 per cent) in those with squamous primaries; four (44 per cent) in association with upper or middle third lesions and five (56 per cent) in association with lower third or cardia lesions.

As hepatic metastases could be confirmed histologically without laparotomy, all 90 patients investigated were used in the calculation of sensitivity, specificity and accuracy of the three investigative modalities. However, as peritoneal and nodal metastases were confirmed by histology only after laparotomy, only the 65 patients undergoing surgery were considered when calculating the sensitivity, specificity and accuracy of the investigative modalities in detecting these metastases.

Laparoscopy correctly identified 22 of the hepatic metastases with three false negatives and no false positives, giving a sensitivity of 88 per cent, a specificity of 100 per cent and an overall accuracy of 96 per cent (*Table 3*). Of the three false negatives, two were due to failure to visualize one or other lobe of the liver owing to intra-abdominal adhesions as a result of previous surgery and one was due to the posterior location of metastatic deposits. Ultrasound identified 12 of the hepatic metastases, with 13 false negatives and two false positives, giving a sensitivity of 48 per cent, a specificity of 97 per cent and an accuracy of 83 per cent. CT identified 14 hepatic metastases with 11 false negatives and two false positives giving a sensitivity of 56 per cent, a specificity of 97 per cent and an accuracy of 85 per cent. Laparoscopy was significantly more sensitive than either ultrasound ($\chi^2=9·191$, $P<0·01$) or CT scan ($\chi^2=6·349$, $P<0·02$) in detecting hepatic metastases and was also more accurate ($\chi^2=8·889$, $P<0·01$ and $\chi^2=6·859$, $P<0·01$, respectively) than both scanning techniques. There were no statistical differences between ultrasound and CT in detecting hepatic metastases. Twelve of the hepatic metastases were detected by all three tests and two by laparoscopy and CT. Three were missed by all three tests and eight were detected only by laparoscopy. The false positive results of ultrasound and CT were in four different patients and subsequent follow-up by repeat computed tomographic scan failed to show the

Table 3 *Hepatic metastases*

	Laparoscopy	Ultrasound	Computed tomography
True positive: sensitivity (%)	22 (88)*	12 (48)	14 (56)
True negative: specificity (%)	65 (100)	63 (97)	63 (97)
False positive (%)	0 (0)	2 (2)	2 (2)
False negative (%)	3 (3)	13 (14)	11 (12)
Accuracy (%)	96†	83	85

Histologically proven, $n=25$, confirmed absent, $n=65$ *Laparoscopy significantly more sensitive than either ultrasound ($\chi^2=9·191$, $P<0·01$) or computed tomography ($\chi^2=6·349$, $P<0·02$); †Laparoscopy significantly more accurate than either ultrasound ($\chi^2=8·889$, $P<0·01$) or computed tomography ($\chi^2=6·859$, $P<0·01$)

Table 4 *Nodal metastases*

	Laparoscopy	Ultrasound	Computed tomography
True positive: sensitivity (%)	18 (51)*	6 (17)	11 (31)
True negative. specificity (%)	29 (97)	28 (93)	26 (87)
False positive (%)	1 (1·5)	2 (3)	4 (6)
False negative (%)	17 (26)	29 (45)	24 (37)
Accuracy (%)	72*	52	57

Histologically proven, $n=35$; confirmed absent, $n=30$. *Laparoscopy significantly more sensitive than ultrasound ($\chi^2=9\cdot130$, $P<0\cdot01$) and more accurate than ultrasound ($\chi^2=5\cdot535$, $P<0\cdot05$) but not significantly better than computed tomography ($\chi^2=3\cdot618$, $0\cdot05<P<0\cdot1$; $\chi^2=3\cdot364$, $P>0\cdot05$, respectively)

Table 5 *Peritoneal metastases*

	Laparoscopy	Ultrasound	Computed tomography
True positive. sensitivity (%)	8 (89)	2 (22)	0 (0)
True negative (specificity, %)	56 (100)	56 (100)	56 (100)
False positive (%)	0 (0)	0 (0)	0 (0)
False negative (%)	1 (1·5)	7 (11)	9 (14)
Accuracy (%)	98	89	–

Histologically proven, $n=9$; confirmed absent, $n=56$

development of metastatic deposits which might have indicated detection of occult hepatic metastases at first investigation.

Peritoneal and nodal metastases were only confirmed histologically if laparotomy was performed. Of the 65 patients having surgery, 35 had histologically confirmed intra-abdominal nodal metastases (*Table 4*). In 21 of these patients (60 per cent) the nodes involved were around the coeliac axis. Laparoscopy identified 18 of the 35 with 17 false negatives and one false positive. Ultrasound detected only six, with 29 false negatives and two false positives; CT detected 11 with 24 false negatives and four false positives. The sensitivities were therefore 51, 17 and 31 per cent, the specificities 97, 93 and 87 per cent, and the overall accuracies 72, 52 and 57 per cent for laparoscopy, ultrasound and CT, respectively. Laparoscopy was statistically more sensitive ($\chi^2=9\cdot130$, $P<0\cdot01$) and more accurate ($\chi^2=5\cdot535$, $P<0\cdot05$) than ultrasound in detecting nodal metastases. The differences between laparoscopy and CT, however, although favouring laparoscopy, just failed to reach statistical significance at the 5 per cent level ($\chi^2=3\cdot618$ and $\chi^2=3\cdot364$, $P>0\cdot05$). There were no differences between ultrasound and CT in the sensitivity or accuracy in detecting nodal metastases.

Nine patients had peritoneal metastases proved at laparotomy (*Table 5*). Of these, eight were correctly identified before operation by laparoscopy with no false positives and one false negative in a patient with metastatic deposit on the inferior surface of the transverse mesocolon. The sensitivity of laparoscopy was 89 per cent, the specificity 100 per cent and the accuracy 98 per cent. Ultrasound demonstrated free intra-abdominal fluid in two patients but no definite metastatic deposits, and CT failed to detect any of the peritoneal metastases.

There was no morbidity or mortality associated with laparoscopy

Discussion

The accurate assessment of intra-abdominal dissemination of malignancy is of considerable importance both in tumour staging and in planning therapeutic strategies. Over the years a great deal of attention has been given to the preoperative detection of hepatic metastases. Biochemical tests of liver function including serum levels of alkaline phosphatase, transaminases and γ-glutamyl transferase are relatively easy to perform and with increasing automation have become widely available. However, their role in the accurate assessment of liver metastases would seem to be limited[13–15].

The results of isotope scanning for detecting liver metastases are rather conflicting. Lamb and Taylor[16] in 1982 found that both liver scintiscans using technetium–sulphur colloid and ultrasound were 97 per cent accurate in determining the presence or absence of liver metastases in 100 patients with colorectal cancer of whom 15 had proven hepatic metastases. Most other authors, however, have reported accuracies of the order of 64–80 per cent for hepatic scintiscans[8,17–19].

Ultrasound scanning, and particularly grey scale ultrasound, has become increasingly available and when used to enhance the diagnostic accuracy of scintiscans has been shown by Sullivan *et al.*[20] to have an accuracy of 93 per cent. Apart from Lamb and Taylor[16], who showed a 97 per cent accuracy, other authors have not been able to reproduce this level of accuracy, but figures of 75–80 per cent have been reported[1,15,17].

It was thought, with the advent of CT, that other scanning techniques might be superseded but several studies have demonstrated that overall accuracy in determining the existence of hepatic metastases is still only in the order of 80–85 per cent[15,17]. Smith*et al.*[17] compared the accuracy of scintiscan, ultrasound and CT in patients with a variety of primary tumours with potential hepatic involvement and found little difference in accuracy in the three techniques, with scintiscans and ultrasound both 80 per cent, and CT 84 per cent accurate. They concluded that lesions <3 cm in diameter were liable to be missed by all three techniques and that direct visualization and biopsy were the only means of making a definitive diagnosis of hepatic metastases. Kemeny *et al.*[15] found a sensitivity of 87 per cent for CT combined with carcinoembryonic antigen levels, but overall accuracy was only 64 per cent for this combined method of assessment.

Scanning techniques are highly dependent on the availability of sophisticated equipment and experienced observers to operate them. Both ultrasound and CT are still evolving and it could be expected that accuracy will steadily increase. However, it is unrealistic for every unit to be abreast of the latest developments of scanning technology and accuracy is still dependent to a great extent on the skill and experience of the observer using the equipment. Neither biochemical tests nor scanning techniques address the problem of other intra-abdominal metastases, particularly peritoneal seeding.

Laparoscopy is widely used as a diagnostic and therapeutic tool in gynaecology, but is relatively little used in general surgery. Its value has been assessed in a number of clinical areas, including the staging of primary intra-abdominal tumours, the evaluation of metastatic disease, and the diagnosis of jaundice and abdominal pain. Complications under either local or general anaesthesia have been few[1,4,5,9] and diagnostic accuracy has been high. Although it has been found to be of little value in the diagnosis of unexplained abdominal pain[5,7,9], it has contributed to the elucidation of the cause of jaundice[4,5,7] where other less invasive tests have not been diagnostic. The staging of pancreatic and other intra-abdominal tumours has been improved using laparoscopy[3,10], and accurate evaluation of the condition of the liver in patients with primary bronchial, breast and lymphoid tumours has been well documented[6,8]. One of the major benefits of laparoscopy has been the opportunity to obtain tissue samples accurately under direct vision not only from the liver but also from nodal or peritoneal metastases, often confirming or refuting the results of other non-invasive investigations. It has also been found to be useful in evaluating the stage of tumours amenable to treatment by chemotherapy or radiotherapy, e.g. lymphomas and ovarian or other gynaecological malignancies[8].

Laparoscopy has been evaluated in the management of patients with gastric cancer with somewhat conflicting results. Shandall and Johnson[1] found laparoscopy of doubtful value in patients with gastric cancer because a high proportion required palliative surgery, whereas Gross *et al.*[2] found it beneficial in avoiding unnecessary surgery. Clearly the location of the primary lesion and the patient's symptoms are important in that those with distal lesions causing pyloric obstruction and vomiting may well require palliative gastroenterostomy whereas those with proximal lesions and dysphagia may not benefit from surgery but may be palliated by non-operative methods.

Few studies have evaluated laparoscopy in relation to tumours of the oesophagus or cardia[1,12] and there are no comparative studies of ultrasound, CT and laparoscopy in evaluating this group of patients.

In our study the results of ultrasound and CT in determining liver status were similar to those reported by others, with overall accuracies of 83 and 85 per cent, respectively. Laparoscopy performed significantly better, with an overall accuracy of 96 per cent, was associated with no mortality or morbidity and allowed histological confirmation of metastases. The three false negative results with laparoscopy were caused by intra-abdominal adhesions in two cases and the posterior location of metastases in one case. Although it is conceivable that some of these technical problems could be overcome by manoeuvres such as inserting the laparoscope in different quadrants of the abdomen, or using instruments to break down adhesions, we must accept that there will be a failure rate for laparoscopy as well as for scanning techniques. It is of note that the metastases in these three cases were also missed by both ultrasound and CT. Of the 25 hepatic metastases, 12 were detected by all three modalities. CT and ultrasound have equally high specificity (97 per cent); therefore positive results can be relied upon. Laparoscopy is probably not required in this situation unless histological confirmation of metastases is desired. CT detected two more patients with hepatic metastases than ultrasound, and may therefore have a slight advantage. However, this is probably offset by the increased cost of the investigation. As eight patients with negative ultrasound and CT were found to have hepatic metastases at laparoscopy (i.e. 32 per cent of all proven hepatic metastases) this is clearly a useful additional investigation if either of these scanning techniques is reported as negative.

Ultrasound and CT perform poorly with regard to nodal metastases, but laparoscopy was not significantly superior to CT although it was significantly better than ultrasound. Metastatic deposits may often be present in nodes that are only slightly if at all enlarged and may therefore not be visible on scan at the present limits of resolution. It may be possible to identify smaller nodes at laparoscopy, but they may or may not contain tumour and a significant proportion may be located only around the coeliac axis and therefore may not be visible by standard laparoscopic techniques. On the whole, nodal metastases are of lesser importance in determining resectability of tumours of the oesophagus or cardia compared with liver metastases or peritoneal metastases, but knowledge of their status may be of importance in staging of disease in patients who are refused surgery on other grounds.

Peritoneal metastases, however, are of considerable importance as their presence will usually preclude major resectional surgery. Although ultrasound demonstrated free peritoneal fluid in two cases, neither ultrasound nor CT demonstrated any of the peritoneal metastases in nine patients. Laparoscopy was positive in eight of these nine patients. Had punch biopsy been available histological proof could have been obtained, but some of these patients required laparotomy for Celestin intubation. The lesions missed in the final patient were located on the inferior surface of the transverse mesocolon. This area is not visualized by standard laparoscopic techniques but may be seen using the techniques described by Cuschieri and Berci[21].

It is worthy of note that 51 per cent of the patients with upper and middle third lesions had intra-abdominal metastases, a figure similar to the 58 per cent of patients with lower third or cardia lesions. It is clearly worth pursuing intra-abdominal dissemination even in patients with lesions high in the oesophagus if unnecessary surgery is to be avoided. The high incidence of metastatic disease in the present group of patients reflects the availability of palliative techniques in this unit and therefore influences the referral practice.

In patients with carcinoma of the oesophagus or cardia laparoscopy offers an accurate, reliable and safe method of preoperative assessment. We would hope that by using laparoscopy in conjunction with the non-operative methods of palliation, unnecessary surgery could be avoided in a significant proportion of patients with malignant dysphagia.

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Cryotherapy for liver metastases: a new approach

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A new system designed for cryosurgery of liver metastases is described. The cryoprobe, which utilizes circulating liquid nitrogen and produces a spherical iceball around each metastasis, is controlled by operative ultrasound. There was nor mortality and all patients left hospital within 10 days. Cryotherapy produced an area of destruction within the liver substance which decreased in size by 6 weeks as shown on serial computed tomographic scanning.

Keywords: Hepatic metastases, cryosurgery, intraoperative ultrasound

Cryotherapy has been used for the treatment of many benign and malignant conditions[1]. Neoplasms of the skin, rectum, bone and larynx have been successfully treated[2–5]. Cryotherapy has also been used for the treatment of liver tumours but using techniques which result in the destruction of a large amount of surrounding liver parenchyma[6,7]. We have designed a system which uses a new type of cryoprobe enabling the freezing of intrahepatic lesions to be performed with only the destruction of a small rim of normal liver tissue around each lesion.

Patients and methods

Seven patients (median age 56 years, range 46–61 years) with liver metastases (six from colorectal cancer, one from carcinoid) have undergone hepatic cryotherapy using a newly designed cryoprobe with an insulated 5 mm diameter shaft (Cryogenic Technology Ltd., Ripley, UK). Within the tip of the probe liquid nitrogen is circulated at −196°C. In each patient the liver was mobilized at laparotomy and following bimanual palpation intraoperative ultrasound was performed using a Bruel and Kjaer (Nærum, Denmark) ultrasound apparatus 1846 and intraoperative ultrasound probe 8537 which incorporates a 7 MHz transducer.

The tip of the probe was passed into the centre of each metastasis using intraoperative ultrasound to localize impalpable lesions (*Figure 1*). The frozen area or iceball created was easily imaged by intraoperative ultrasound, appearing as a dark (hypoechoic) area (*Figure 2*), the size of which could be monitored. Freezing was continued until the diameter of the iceball was 1 cm greater than that of the metastasis. Thawing was then commenced by circulating nitrogen at room temperature down the probe and after several minutes the probe could be removed from the frozen metastasis. The track was packed with oxidized cellulose to prevent bleeding. Prophylactic antibiotics were given to all patients. Postoperative computed tomographic (CT) scans were performed on all patients and they were observed closely in the outpatient department for adverse effects of the treatment.

Results

Thirty-nine metastases were identified in the seven patients (range 3–12 metastases per patient). Eight metastases were impalpable and only detected by intraoperative ultrasound. The diameter of lesions ranged from 0·3 cm to 6·5 cm and the time for freezing from 1 min to 36 min.

All patients made an uncomplicated postoperative recovery and were discharged home 7–10 days after surgery. The effect of this treatment was monitored by CT scan. *Figure 3* shows one impalpable metastasis before operation, 3 days after operation and 6 weeks after operation. Cryotherapy produced an area of destruction within the liver substance which often contained some gas from tissue necrosis (*Figure 3***b**). After 6 weeks this area of necrosis had decreased in size.

No adverse effects have been observed during the follow-up period which ranges from 1 to 6 months. The patient with carcinoid has had total relief from his symptoms of flushing and diarrhoea. Of the patients with colorectal metastases, four have been followed up for more than 3 months. In three patients serum carcinoembryonic antigen concentrations fell following cryotherapy and in one of them serum carcinoembryonic antigen had fallen from 4·6 μg/l before cryotherapy to < 1·5 μg/l 2 months later. However, it is too early to comment on the actual benefit derived by these patients.

Discussion

The safety and benefit of hepatic resection for patients with less than four unilobar metastases from colorectal cancer are well established. An acceptable operative mortality rate for major resection of about 5 per cent is expected, and up to 35 per cent

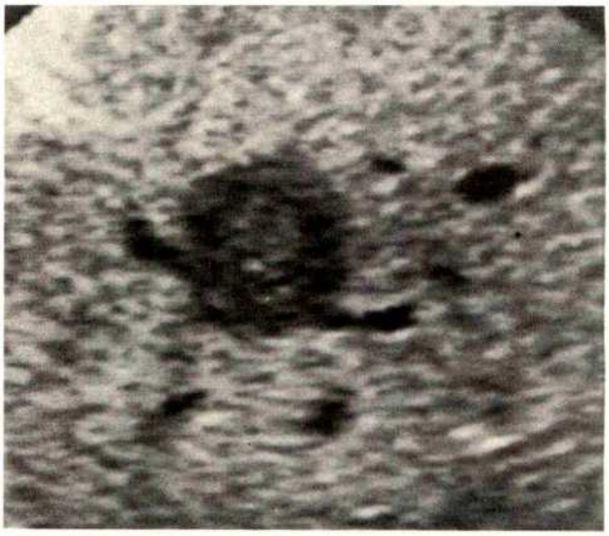

Figure 1 *Intraoperative ultrasound scan of an impalpable liver metastasis*

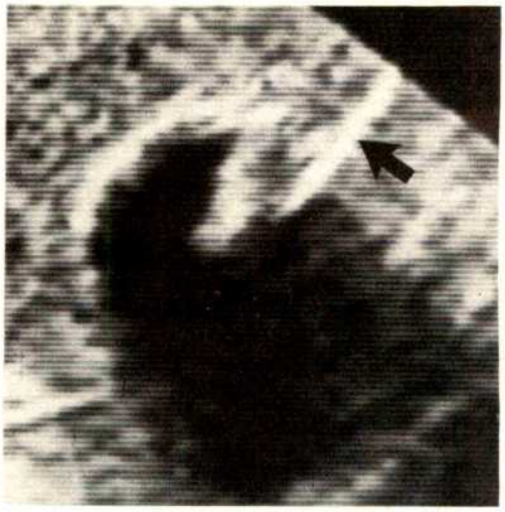

Figure 2 *Intraoperative ultrasound scan demonstrating cryoprobe (arrowed) and iceball which casts an acoustic shadow*

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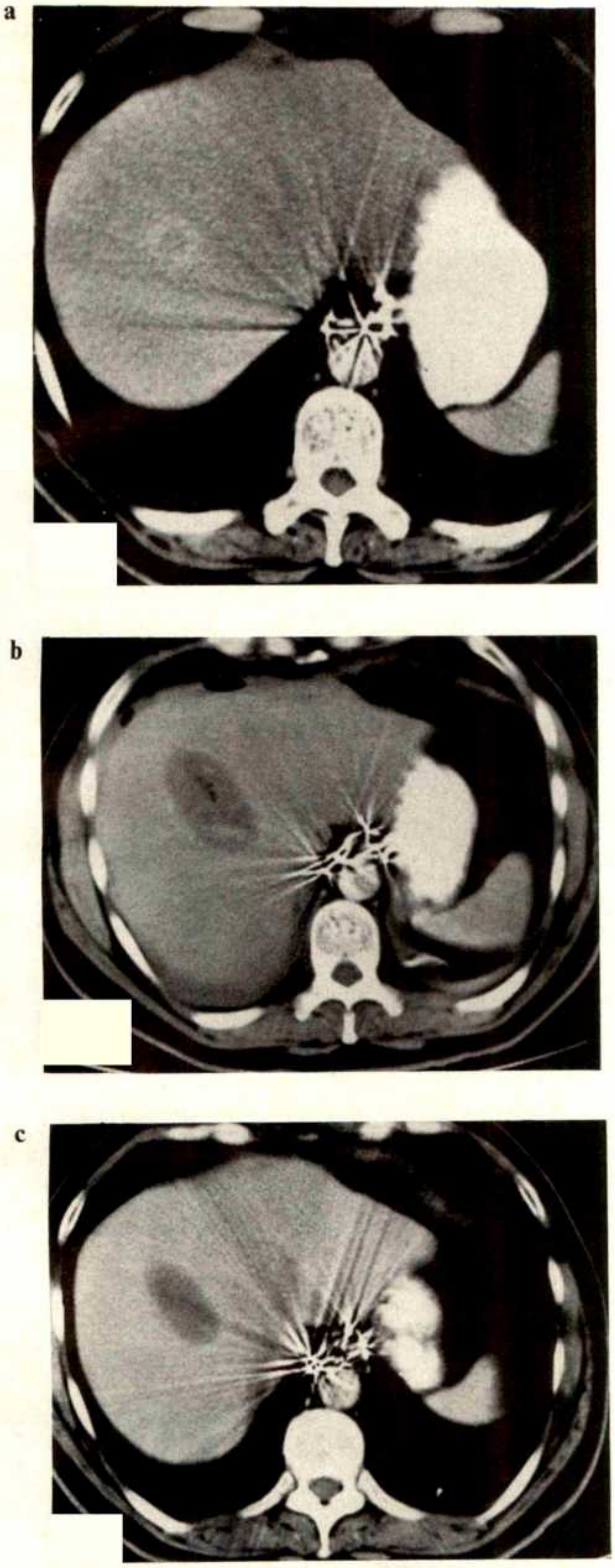

Figure 3 *Computed tomographic scan of impalpable metastasis,* **a** *before cryotherapy,* **b** *3 days after cryotherapy (showing an area of necrosis with central gas formation) and* **c** *6 weeks after cryotherapy when some resolution can be seen*

of patients undergoing successful resection can expect to live 5 years[8]. For patients with unresectable disease systemic chemotherapy has proved to be disappointing and regional chemotherapy, although producing response rates of 70 per cent in some centres, is accompanied by an unacceptable level of serious complications in most series[9,10].

Cryosurgery is an established technique for the treatment of many benign and malignant lesions[1–5]. Previous attempts at cryosurgery for hepatic malignancy have involved the use of either a surface probe with a central spike down which cold is conducted so producing at best a cone shape of liver destruction, or surface application of a hollow plate-like probe which is only suitable for the destruction of superficial lesions. Using these techniques, impressive results for hepatic cryosurgery have been described[6,7]. The circulating liquid nitrogen probe which we have used has the advantage of delivering a temperature of −196°C to the lesion with destruction of only a rim of normal liver tissue around each lesion.

The technique of intraoperative ultrasound allows the detection of more metastases than is possible using conventional abdominal ultrasound or CT scanning[11] and also allows localization of lesions to be carried out at laparotomy. Impalpable lesions as small as 5 mm in diameter may be detected. These small impalpable metastases often make a patient's disease unresectable. In such a case, cryosurgery using the circulating liquid nitrogen probe has the potential to destroy all detectable metastases, with minimal destruction of surrounding hepatic parenchyma. In addition it has been demonstrated previously that large blood vessels tolerate freezing extremely well because the passage of warm blood causes dissipation of the freezing process so reducing tissue damage close to the vessel wall[12]. Cryosurgery, therefore, may be able to destroy lesions that have been deemed to be unresectable because of their proximity to large veins.

It is acknowledged that the effect on survival of patients treated by cryotherapy using this new system has not yet been studied but this treatment is easily performed, is well tolerated and certainly produces radiological evidence of necrosis. Its role in palliation and possible improvement in survival time clearly requires investigation.

Acknowledgements

We are grateful to Mr Brian Clarke and Mr Philip Shepherd of Cryogenic Technology Ltd. who have co-operated with us in developing the cryoprobe.

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Resectability of large focal liver lesions

Despite modern imaging techniques evaluation of the resectability of large focal liver lesions is often difficult or impossible until the time of operation. Based on experience with 54 primary or secondary focal liver tumours, a simple morphological classification has been found to be reasonably predictive of resectability. All tumours were classified before operation using computed tomography, ultrasound and angiography; 38 patients underwent laparotomy. Dependent, 'hanging' tumours (n = 7) were resected in six cases, expansively growing 'pushing' tumours (n = 19) were resected in 18 cases, and infiltrating, 'invasive' tumours (n = 17) were not resected because of involvement with major vascular structures. Eleven small tumours (< 5 cm) were not classifiable by this system. This simple classification may be a useful clinical concept in preoperative assessment of resectability of focal liver lesions. Hanging tumours should always be resected, and large expansile tumours are generally resectable despite their size. Invasive tumours can only be resected in exceptional cases.

Keywords: Hepatic resection, liver tumours, liver surgery

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Preoperative assessment of resectability in large focal primary or secondary benign or malignant liver tumours remains a difficult challenge. The actual resectability rate depends on the skill and experience of the individual surgeon and on referral patterns in specialized hepatobiliary clinics. In general, few liver malignancies are resectable. For example, only 5 per cent of hepatic metastases from colorectal cancer have been found to be resectable[1] and nearly 50 per cent of patients specifically referred for hepatic resection to hepatobiliary clinics will not come to actual resection[2]. However, the widely accepted criteria of irresectability such as bilobar involvement, vessel infiltration and very large tumour size are no longer unquestioned. In particular, tumour size alone does not appear to be a contraindication to hepatic resection[3–9].

Standard imaging techniques provide valuable and detailed information about the resectability of large focal malignant or benign tumours. Despite increasingly refined methods of computed tomography, ultrasonography, hepatic angiography, late phase portography and inferior cavography, definitive preoperative evaluation of resectability in large lesions with involvement of the hilus or of the retrohepatic vena cava is difficult or impossible, and the question of resectability often remains open until the time of surgery.

This study investigates a simple clinical concept of tumour morphology in the preoperative assessment of focal liver lesions. Based on clinical experience and observation of a large number of liver lesions, a simple classification is proposed which has been found to be useful in the preoperative assessment of large focal liver tumours.

Materials and methods

Three different morphological varieties of tumour are defined as follows.

'Hanging' tumours

These tumours grow with a base adjacent to the free liver edge and hang in their entirety, or at least their major part, free of the rest of the surrounding liver tissue in the abdominal cavity. Some of these tumours can be literally pedunculated[10]. *Figures 1* and *2* demonstrate a typical hanging tumour.

'Pushing' tumours

These tumours grow expansively and compress the surrounding normal liver tissue. Even in malignant tumours there is usually a rim of compressed atrophic liver parenchyma forming a pseudocapsule or at least a well-defined plane between the malignant and the surrounding benign tissue. The pushing tumours can grow to be very large, involving nearly the whole liver (*Figures 3* and *4*).

'Invasive' tumours

These tumours, which can be very large, grow without anatomical limits and no clear margin or rim of compressed pseudocapsule is formed so that differentiation of normal from malignant areas of the liver is difficult (*Figure 5*).

Small tumours, < 5 cm in diameter, cannot be properly classified within this system because they do not display gross morphological differences.

We have investigated prospectively the resectability of all liver tumours referred to our clinic from October 1986 to September 1988. All primary benign or malignant focal tumours and liver metastases excluding haemangioma were considered. The tumours were preoperatively classified by the senior surgeon and radiologist generally on the basis of a computed tomographic scan and an angiogram. A total of 54 primary or secondary focal liver tumours (*Table 1*) were assessed by imaging techniques (ultrasonography, computed tomography, angiography, late phase portography or inferior vena cavography). According to the preoperative clinical classification in these 54 patients, we identified 19 pushing, seven hanging, 17 invasive, and 11 tumours too small to be classified. Of these, 37 lesions were considered resectable

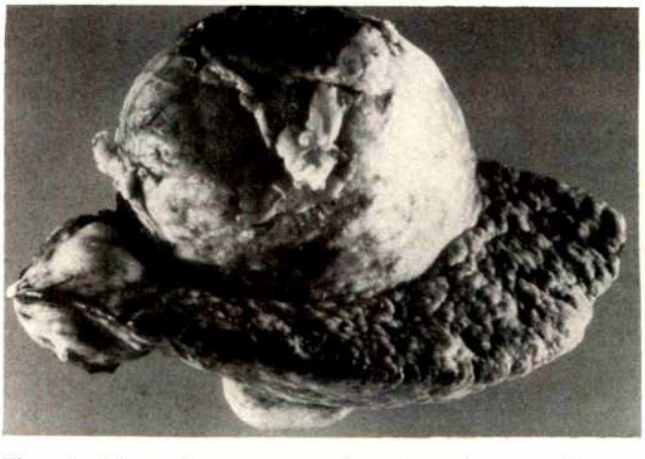

Figure 1 *'Hanging' tumour: resected specimen of a typical hanging lesion of a primary hepatocellular carcinoma in a 72-year-old patient with liver cirrhosis*

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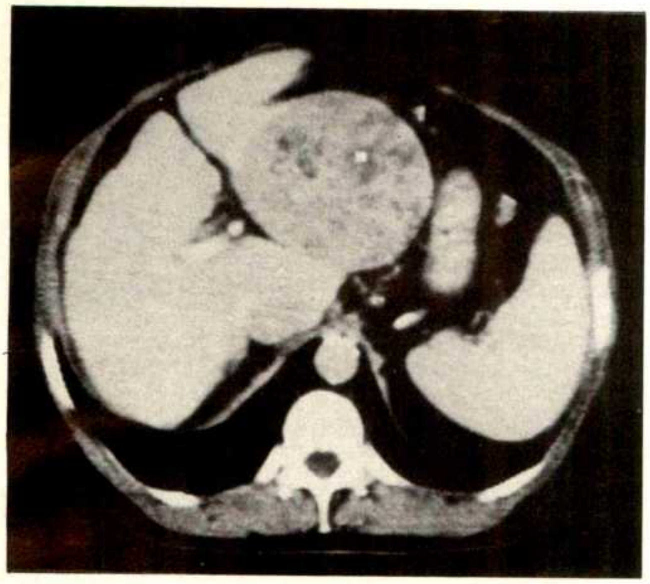

Figure 2 *'Hanging' tumour: ultrasound image demonstrating the dependent nature of the tumour. The spherical lesion appears to be free within the abdominal cavity*

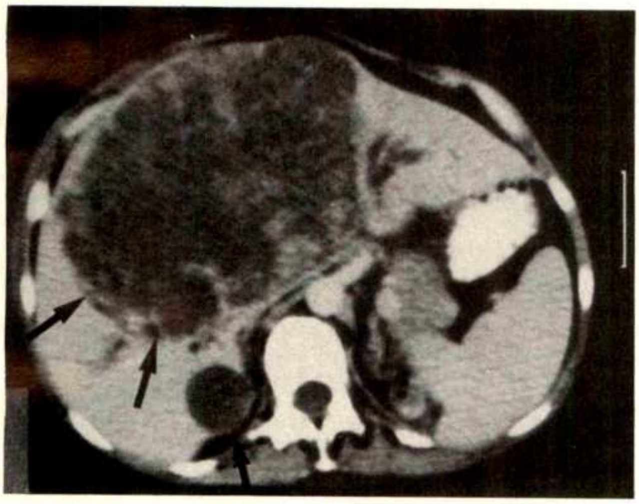

Figure 3 *'Pushing' tumour: metastasis of a hypernephroma in a 33-year-old woman. This is a typical example of a well defined malignant lesion occupying almost the entire liver (arrows) apart from the posterior sector of the right side. The tumour was resected by extended left hepatectomy; the patient is alive 2 years later*

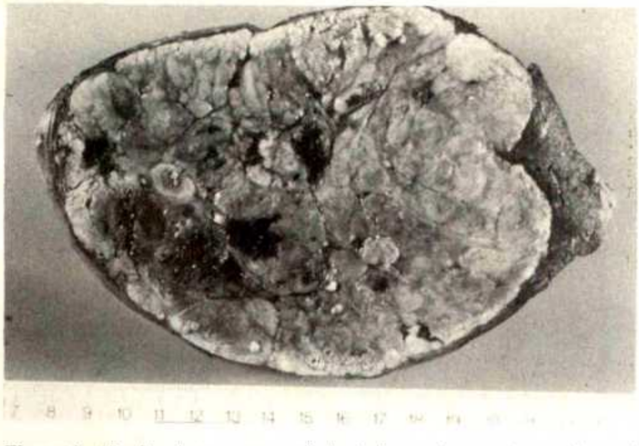

Figure 4 *'Pushing' tumour: pathological specimen of a colorectal metastasis in the liver of a 51-year-old man. The small frame of compressed liver tissue forms a pseudocapsule*

and the patients underwent laparotomy. An additional patient underwent laparotomy for hepatic artery ligation (see below). The intraoperative findings in the 38 laparotomized patients confirmed the preoperative classification in all cases.

Results

From a total of 54 patients 37 underwent laparotomy for possible tumour resection. Of 19 expansively growing tumours (pushing tumours), 18 were resectable. One expansile hepatocellular tumour involving the right lobe and segment IV of the left lobe of the liver in a 70-year-old patient was, before operation, considered to be technically removable. However, because of his age and poor general health laparotomy for resection was not initially performed. Embolization was attempted but failed because of anatomical vascular problems. The patient was subsequently explored surgically for planned hepatic artery ligation.

Of the seven dependent, hanging tumours six were resected. An hepatocellular carcinoma infiltrating the transverse colon of a 70-year-old patient was not removed surgically; although a resection appeared technically possible, it was doubted whether a combined resection of the liver and colon could be tolerated by the patient. This judgement sadly proved true, as the combined resection was later performed in another hospital after which the patient succumbed.

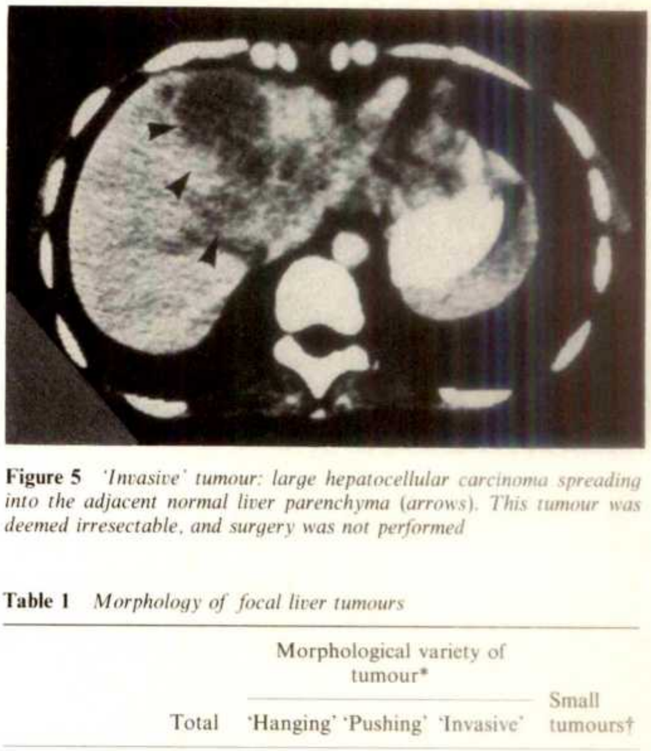

Figure 5 *'Invasive' tumour: large hepatocellular carcinoma spreading into the adjacent normal liver parenchyma (arrows). This tumour was deemed irresectable, and surgery was not performed*

Table 1 *Morphology of focal liver tumours*

	Total	Morphological variety of tumour*			Small tumours†
		'Hanging'	'Pushing'	'Invasive'	
Primary‡					
Hepatocellular carcinoma	24	6	3	14	1
Adenoma	1	1			
FNH	1		1		
Metastases					
Colorectal	21		11	1	9
Stomach	1				1
Kidney	1		1		
Carcinoid	2		2		
APUD	2		1	1	
Unknown	1			1	
Total	54	7	19	17	11

* The morphological varieties of tumour are described in the 'Materials and methods' section; † small tumours cannot be classified because they do not display gross morphological differences; ‡ Primary liver tumours; FNH, focal nodular hyperplasia

Table 2 *Preoperative classification and resection status of liver*

	Total	Morphological variety of tumour*			Small tumours†
		'Hanging'	'Pushing'	'Invasive'	
Preoperative classification	54	7	19	17	11
Laparatomy for resection	37	7	18	1	11
Actual resection	33	6	18	0	9

* The morphological varieties of tumour are described in the 'Materials and methods' section; † small tumours cannot be classified because they do not display gross morphological differences

Only one infiltrating invasive tumour was assessed as resectable before operation: during the operation it proved to be irresectable due to infiltration of vital structures. In the other 16 patients with invasive tumours, laparotomy for resection was not performed as these lesions were not considered resectable by radiological assessment. Two of the patients underwent hepatic artery ligation and one an embolization procedure.

In all, nine of the 11 tumours too small to be classified were removed; the other two were not resected because previously undetected diffuse small liver metastases were found at the time of operation.

The dependent hanging variety of tumour was only encountered with hepatocellular carcinoma. The majority of invasive tumours were also hepatocellular in origin, while most of the pushing expansile tumours were metastatic. It is of interest to note that of 38 patients preoperatively considered to be resectable only five were not. In this series there was one postoperative death, 24 h after laparotomy, in a patient with a metastatic 'APUD' lesion. The overall resectability rate was therefore 61 per cent (33 of 54 cases), and 86 per cent of those lesions preoperatively assessed as resectable by this clinical classification were ultimately successfully resected (33 of 38 cases).

Discussion

There are no clearly defined and uniformly accepted criteria that determine resectability of large benign or malignant liver tumours. Preoperative assessment of resectability is of value but, even with modern imaging techniques such as ultrasonography, computed tomography, angiography, cavography and portography, the ultimate resectability of a given lesion often remains uncertain until operation. This is especially true for large liver lesions where the lack of clear criteria about whether a tumour can be resected or not may lead either to unwarranted laparotomy in unsuitable cases or withholding of an operation because of incorrect preoperative judgement of irresectability. Simple criteria which may allow a clear definition of the possibility of resection were therefore sought. The classification that was developed is based on the gross morphological appearance of liver tumours as displayed by ultrasonography, computed tomography and angiography. It has been found to be reasonably predictive of resectability. Of the 38 patients classified as resectable based on preoperative assessment, 37 underwent laparotomy with the intention of resection and 33 ultimately underwent resection. Two further cases were technically resectable but because of the poor general condition of the patients and/or local invasion of the tumour surgery was not undertaken. Indeed, from a technical point of view, all 19 expansile pushing tumours and all dependent hanging tumours were resectable despite their often considerable size, while all large invasive tumours were not resectable.

Hanging tumours should always be explored and may often be resected without formal anatomical procedures by simply amputating the small rim of liver tissue connecting the dependent mass to the liver. This point is important to recognize. Because only minimal amounts of uninvolved liver tissue is removed, such procedures may be tolerated even in patients with decreased overall liver function due to cirrhosis. Large expansile pushing tumours are resectable surprisingly frequently and the experienced hepatobiliary surgeon should not be deterred from exploration of these patients for resection, despite the often intimidating size of such tumours. Invasive tumours can only be resected in exceptional cases and therefore exploration should rarely be performed.

We would not expect this observed pattern of behaviour of large focal liver tumours to carry any significant biological implication given the heterogeneity of tumour types included for analysis. It must be noted that the distinction between pushing, hanging and invasive tumours may occasionally be difficult to determine in individual cases, although in our experience the preoperative impression generally proved accurate in predicting the findings at laparotomy. The proposed classification may certainly be criticized as being somewhat artificial. None the less, this clinical concept may provide a useful framework with which to approach the problem of resectability.

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Alkaline battery-induced tracheo-oesophageal fistula

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The rapid propagation of small electronic gadgets and toys controlled by alkaline batteries has brought these potentially lethal objects within the reach of small children whose natural instinct is to put everything into the mouth. Tracheo-oesophageal fistula caused by alkaline battery ingestion is a rare complication but highlights the hazards of ignoring these foreign bodies.

Case report

A 16-month-old girl was admitted with dysphagia of 4 weeks' duration. Chest radiography showed a coin-shaped foreign body in the upper oesophagus (*Figure 1*), which was removed endoscopically. The object was a 1-cm diameter watch battery which the child had swallowed several weeks earlier.

Postoperatively, the child continued to have feeding problems which failed to resolve with nasogastric feeds. A barium swallow showed a large tracheo-oesophageal fistula at the level of the thoracic inlet (*Figure 2*). Nasogastric feeding was continued, and chest physiotherapy and antibiotics were commenced to improve her nutritional and respiratory status.

Three weeks later, via a right-sided cervical approach, a 1-cm diameter fistula was found between the trachea and the oesophagus. The fistula was divided and the defects repaired with 4–0 silk sutures. A postoperative oesophageal leak closed spontaneously, and a repeat contrast study was satisfactory. Oral feeding was re-established, but 6 weeks later the child was readmitted with a radiologically confirmed recurrent fistula.

Re-exploration revealed a 3-mm diameter tracheo-oesophageal fistula which was divided. The trachea and oesophagus were completely separated over a 5-cm length and the defects were repaired with 4–0 polydiaxonone sutures. A 5-cm square patch of GORE-TEX® (W. L. Gore and Associates Incorporated) was laid in between the trachea and oesophagus and was sutured to the trachea.

A temporary oesophageal leak occurred after operation but a contrast study 6 weeks later failed to detect recurrence of the fistula. The symptoms of coughing with feeds persisted and a repeat study confirmed a second recurrence of the tracheo-oesophageal fistula. The child was then referred to the Hospital for Sick Children, Great Ormond Street, for further management.

The recurrence of the tracheo-oesophageal fistula was confirmed endoscopically. A ureteric catheter was passed into the oesophagus through the fistula at bronchoscopy, via a transverse cervical incision; the trachea and oesophagus were exposed with considerable difficulty because of dense fibrosis and the fistula was identified. The tracheal defect was repaired with interrupted 4–0 Prolene® (Ethicon Ltd., Edinburgh, UK) sutures. A 3-cm length of oesophagus including the fistula was resected and an end-to-end anastomosis was performed in two layers with 4–0 polyglycolic acid sutures. Omohyoid muscle was mobilized and placed between the trachea and oesophagus.

Repeat endoscopy at 3 weeks confirmed successful repair. The child remains symptom-free 9 months after operation.

Discussion

Oesophageal perforations can be caused by batteries, leading to severe mediastinitis and occasionally to exsanguinating haemorrhage. Foreign bodies that pass into the stomach are expected to be excreted without incident. Alkaline batteries, however, need close observation as they have a tendency to open and cause alkaline erosion and even perforation of the stomach.

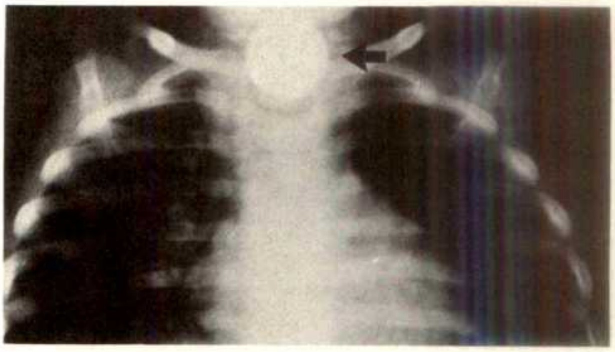

Figure 1 *Plain radiograph of the chest showing the foreign body lodged at the thoracic inlet*

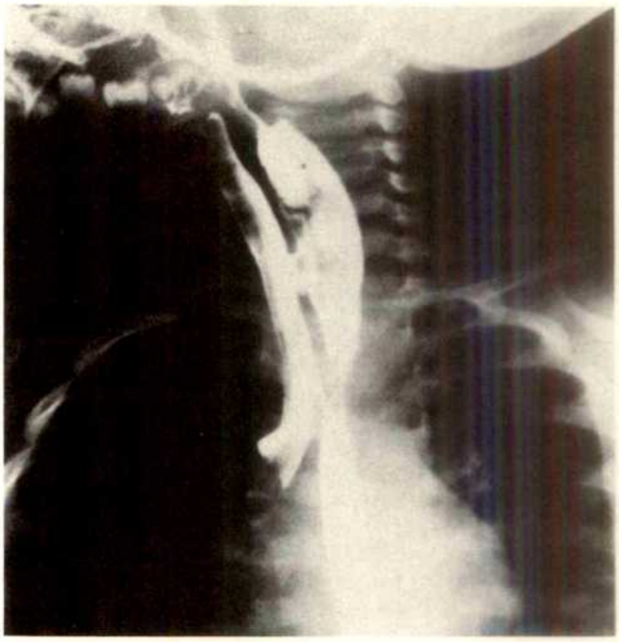

Figure 2 *Contrast swallow showing the large tracheo-oesophageal fistula*

Tracheo-oesophageal fistula caused by a foreign body is rare, and of six cases previously reported only one was due to an alkaline battery[1,2]. An additional case has been reported where a large fistula was found at necropsy in a child who died from severe mediastinitis and haemorrhage following alkaline battery ingestion[3]. Alkaline battery ingestion is a true emergency and, if lodged in the oesophagus, the battery must be promptly removed by endoscopy.

Repair of an acquired corrosive tracheo-oesophageal fistula by simple closure is unsuitable as the adjacent tissue is also affected. Wide excision is recommended if recurrence is to be avoided.

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Bile leaks after simple cholecystectomy

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Drains after cholecystectomy are used commonly to avoid biliary leaks and subsequent peritonitis. Thirty-five patients who had had cholecystectomy without drainage underwent ^{99m}*Tc-labelled dimethylphenylcarbamoylmethyliminodiacetic acid (HIDA) and ultrasound scans the morning after surgery. Biliary leaks detected by positive HIDA scans occurred in 11 patients. Subhepatic fluid collections were seen on 20 ultrasound scans. There was no relation between biliary leaks and subhepatic collections. Many of the collections were not seen on the HIDA scan, suggesting that they contained blood and not bile. Many of the patients with bile leaks showed no fluid collection. Clinical complications were few and evenly distributed between those with positive and negative scans. We conclude that bile leaks are not an occasional event but occur after 31 per cent of undrained cholecystectomies and that these bile leaks remain clinically unimportant.*

Keywords: Cholecystectomy, bile, peritonitis, drain

The debate about whether drains should be employed after elective cholecystectomy continues and conflicting results have been reported[1–5]. Recent studies and opinion have favoured the omission of drains[4–6]. Nevertheless, the majority of surgeons continue to employ drains even for uncomplicated cholecystectomy[7]. The main reason for this continuing practice is the fear of leakage after operation[8,9]. Drains are placed routinely by many surgeons to catch the occasional leak, although the incidence and significance of bile leakage after cholecystectomy remains unknown. It is known, however, that loculated fluid collections occur in the subhepatic space following simple cholecystectomy[5]. These collections spontaneously resolve and are of little clinical importance. The composition of these collections is not known, although they must contain blood, bile or a mixture of these fluids. The purpose of this study was to investigate the incidence of biliary leaks after elective cholecystectomy in patients not drained after surgery, and to assess the clinical significance of such leaks.

Patients and methods

Informed consent before surgery was obtained in 35 patients undergoing elective cholecystectomy for gallstones: the mean age was 56·4 years (range 27–81 years), and 17 were men. Antibiotic prophylaxis consisted of one dose of cephazolin (1 g) intravenously at induction of anaesthesia. A right upper transverse incision was employed and operative choledochography was performed. A standard antegrade cholecystectomy was undertaken and haemostasis secured with diathermy. No drainage was used and the gallbladder bed was not closed with peritoneum. Patients in whom the operative choledochogram revealed that exploration of the common bile duct was necessary were excluded from the study. The wound was closed with continuous nylon and subcuticular Prolene® (Ethicon Ltd., Edinburgh, UK). Some of the operations were technically difficult and the term simple cholecystectomy was used to denote removal of the gallbladder without other procedures, such as opening the bile duct or duodenum. The length of operation and blood loss were recorded.

At the completion of skin closure 290–330 MBq ^{99m}Tc-labelled dimethylphenylcarbamoylmethyliminodiacetic acid (HIDA) was injected intravenously and the time of the injection was noted.

On the first day after operation a HIDA scan of the whole abdomen was performed using an IGE 400T tomographic γ camera (International General Electric, Slough, UK) linked to a DEC PDP 11/34 computer (Nuclear Diagnostics, North Fleet, UK). The level of radioactivity of ^{99m}Tc-labelled bile in the right upper quadrant and whole abdominal radioactivity were expressed as counts per second (c.p.s.). To allow for the decay of technetium the corrected counts per second were calculated from the formula: c.p.s. $\times\, t_d/t_{\frac{1}{2}} \times 0{\cdot}693^{-e}$, where t_d is the decay time (time elapsed from injection of radionuclide to performance of scan), $t_{\frac{1}{2}}$ is the half-life of ^{99m}Tc, and e is the exponential. Scans were interpreted by an independent specialist in nuclear medicine. The leakage of bile into the gallbladder bed was estimated by the right upper quadrant radioactivity expressed as a percentage of whole abdomen radioactivity.

Immediately after the HIDA scan an ultrasound examination of the right upper quadrant was performed and the diameter of any collection measured in two planes. The volume of the collections was estimated by averaging the diameters to obtain the mean radius (r) and using the formula $V = 4\pi r^3/3$.

In one patient with a collection noted on ultrasound, the subhepatic fluid was aspirated and submitted for radioactive analysis using the γ counter.

The complications recorded after operation included respiratory tract and wound infection, unexplained pyrexia and urinary retention. Respiratory tract infection was defined as the production of purulent sputum with fever, and wound infection as purulent discharge from the wound. Unexplained pyrexia was defined as occurring when the patient had a pyrexia of 38°C or more for 24 h or more with no cause detected.

Results

A positive HIDA scan showed radioactivity in the right upper quadrant which was outside the alimentary tract and indicated a leakage of bile during the early postoperative period (up to 16–24 h after surgery). Eleven patients had positive HIDA scans reported. These had a mean right upper quadrant:whole abdomen radioactivity value of 51 per cent (range 22–77 per cent). Negative HIDA scans were found in 24 patients with a right upper quadrant:whole abdomen radioactivity value of 2 per cent (range 0–17 per cent). No recordable right upper quadrant radioactivity was seen in 17 patients, and seven had a mean right upper quadrant:whole abdomen value of 6·8 per cent. Positive HIDA scans indicating bile leaks were demonstrated in ten of 17 men and one of 18 women (*Table 1*). The length of operation was not significantly different in HIDA-positive patients (55 min) compared with HIDA-negative patients (60 min), and blood loss was negligible in all cases. There was no association with a particular surgeon.

Loculated fluid collections demonstrated by ultrasound were present in 20 patients. The mean volume was 17 ml (range 3–113 ml). Collections were equally distributed between the sexes, and the mean ages of patients with or without collections were similar. Operating time was also the same in those with positive and negative ultrasound scans. There was no relationship between HIDA and ultrasound scan results (*Table 2*). Six of 11 patients with positive HIDA scans had no collection

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Table 1 *Age, sex and scan results of patients undergoing elective cholecystectomy*

	Whole group ($n=35$)	HIDA scan Positive ($n=11$)	HIDA scan Negative ($n=24$)	Ultrasound scan Positive ($n=20$)	Ultrasound scan Negative ($n=15$)
Men	17	10	7	9	8
Women	18	1	17	11	7
Mean age (years)	56·4	64·5	52·8	57·0	55·0

HIDA, $^{99\mathrm{m}}$Tc-labelled dimethylphenylcarbamoylmethyliminodiacetic acid

Table 2 *Bile leaks found by HIDA scanning compared with collections detected by ultrasound*

Ultrasound scan	HIDA scan Positive	HIDA scan Negative	Total
Positive	5	15	20
Negative	6	9	15
Total	11	24	35

HIDA, $^{99\mathrm{m}}$Tc-labelled dimethylphenylcarbamoylmethyliminodiacetic acid

Table 3 *Complications in 35 patients after elective cholecystectomy*

	HIDA scan Positive	HIDA scan Negative	Ultrasound scan Positive	Ultrasound scan Negative	Total
Respiratory tract infection	2	3	3	2	5
Wound infection	1	1	0	1	2
Unexplained pyrexia	1	4	2	3	5
Urinary retention	1	0	1	0	1

HIDA, $^{99\mathrm{m}}$Tc-labelled dimethylphenylcarbamoylmethyliminodiacetic acid

detected by ultrasound, and 15 collections were seen in 24 patients whose HIDA scans were negative. Only nine patients had negative HIDA and ultrasound scans.

One HIDA-negative patient with a subhepatic fluid collection detected by ultrasound had this collection aspirated. Serosanguinous fluid was obtained, confirming the ultrasound scan appearances. Analysis of the fluid by a γ counter showed a level of radioactivity similar to background radiation (9·0 *versus* 8·3 c.p.s.), thus confirming the absence of radioactive bile in accordance with the negative HIDA scan.

Postoperative complications occurred with similar frequency in patients with and without a biliary leak or collection (*Table 3*).

Discussion

We have shown that biliary leaks occur in 31 per cent of patients after cholecystectomy, and yet clinically significant bile leakage is uncommon[4,5,10,11]. The method of choice for detecting bile leaks postoperatively is $^{99\mathrm{m}}$Tc-labelled HIDA scanning[12,13]. The gallbladder, common bile duct and early accumulation in the duodenum are visualized within 30 min of intravenous administration. Thereafter, the radioactive label can be seen in the gastrointestinal tract[14]. HIDA is cleared into the bile in 2–3 h and so the kinetics of HIDA excretion suggest that the biliary leaks occur within this time. In this study HIDA was administered at the completion of the operation and it is probable that later administration, such as the next day, would not demonstrate the biliary leaks. The importance of delayed views after injection has been stressed[12,13] and our patients were scanned 16–24 h after surgery. Should there be doubt about the source of right upper quadrant activity, a second scan a few hours later can be performed. Radioactivity within the bowel will move on, but that in a collection remains static. False positive results from the bowel were not a problem in this study and scans were easy to interpret.

The good discrimination in right upper quadrant:whole abdomen radioactivity values between positive (51 per cent) and negative (2 per cent) HIDA scans helps to confirm the accuracy of HIDA scanning in detecting biliary leaks.

Our results indicate that a bile leak after cholecystectomy is not an occasional event but occurs in nearly a third of patients, which is a higher proportion than expected. The apparently higher incidence of bile leaks in men is unexplained. The difficulty of the operation as measured by time and blood loss was similar in HIDA-positive and HIDA-negative patients. The amount of bile leaked could be measured only in terms of right upper quadrant:whole abdomen radioactivity values. This does not give the precise volume of bile that had leaked because of difference in scatter of the γ radiation between patients. Only five of 11 patients with a bile leak had a collection detectable by ultrasound. These collections were small (7–12 ml). It should be noted that 15 of 24 patients without a bile leak had a collection detectable by ultrasound and these collections must be composed of blood or haemoserous fluid. One such collection which was aspirated and analysed for radioactivity supports this suggestion.

The proportion of patients (57 per cent) with a loculated fluid collection after surgery is higher than others have found. In one study no undrained patients had a collection detected by ultrasound after cholecystectomy[11]. We have been able to look for smaller collections using a modern ultrasound scanner with good resolution and have confirmed our findings by needle aspiration.

The lack of correlation between a positive HIDA scan and a positive ultrasound scan was unexpected. Bile is a chemical solution, whereas blood is an organic tissue, and it seems they may be treated differently by the peritoneum.

A strongly positive HIDA scan and a negative ultrasound scan were found in six of 11 HIDA-positive patients. We conclude that pure bile can leak into the peritoneal cavity while blood is localized as a collection in the subhepatic space. Ultrasonography is therefore not a good method of detecting pure bile leakage. We suggest that those five patients in whom both scans were positive had a mixture of bile and blood in the subhepatic space but that it was the blood constituent that caused the collection to form. All our patients were undrained, but previous reports have indicated that drains may influence the composition of leaked fluid and subhepatic collections[5,11].

It is likely that the bile leakage comes from small biliary radicles damaged by dissection of the gallbladder bed. Bile and blood have previously been shown to be readily reabsorbed by the peritoneum[5,8,11]. None of these leaks was clinically significant, and no patient developed a complication specifically related to bile leakage. We suggest that it is the introduction of infection into these harmless bile leaks, as may happen with the placing of a drain, that can render them potentially dangerous.

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Appendicectomy and carcinoma of the caecum

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A total of 519 patients presenting with carcinoma of the caecum in the Plymouth Health District between 1975 and 1987 were reviewed. The clinical course was determined in relation to patients with and without a history of previous appendicectomy. There was no difference in the incidence of previous appendicectomy between patients with carcinoma of the caecum and an age and sex matched control group. The presence of synchronous carcinomas and/or adenomas was unrelated to previous appendicectomy. Ten patients presented with appendicitis and 11 with a mucocele of the appendix as the first sign of carcinoma of the caecum. Previous appendicectomy was associated with a higher incidence of local fixity, invasion of the abdominal wall, metastatic spread and poor differentiation. These differences were reflected in a significantly lower resection rate for carcinomas in patients who had previously undergone appendicectomy. The survival of patients who had previously had appendicectomy was significantly reduced. Four independent prognostic factors for survival were identified using multivariate discriminant analysis. These were Dukes' classification, local invasion, tumour differentiation and previous appendicectomy. Local recurrence was more common in patients who had previously had appendicectomy and was often in the old appendicectomy wound itself. Appendicectomy does not increase the risk of carcinogenesis in the caecum. In this study a history of appendicectomy was an independent risk factor for survival and significantly worsened the prognosis for patients who subsequently developed carcinoma of the caecum.

Keywords: Appendicectomy, carcinoma, caecum.

Colorectal cancer is a major health problem in the western world with over 100 000 new cases and 50 000 deaths attributable to the disease reported each year in the USA[1] There is evidence that the distribution of cancer within the large bowel is changing in the USA, with an increasing proportion of tumours occurring in the right colon and fewer in the rectum[2,3] To date, however, this change has not been noted in the UK where carcinoma of the caecum and ascending colon accounts for from 15 to 25 per cent of all large bowel cancers[4–7]. Carcinoma of the caecum is often locally advanced at presentation and this has been attributed to the relative paucity of symptoms until late in the disease process[4,8–12] Another, and as yet unassessed, reason for these tumours being locally advanced might be previous surgery such as appendicectomy. This study therefore questions the possible association of previous appendicectomy and carcinoma of the caecum in a large, unselected, and consecutive group of patients with these tumours.

Patients and methods

This study includes all 553 patients with carcinoma of the caecum who presented in the Plymouth Health District (population 412 000) from January 1975 to July 1987, inclusive Patients were identified by reference to hospital records, health authority records, discharge summaries, pathology reports, cancer registry office figures, and all coroner's and hospital autopsies The notes of all patients were closely examined by the authors and a record was made of the presentation, past operative history, operative findings, and histology. In 34 patients incomplete information was available leaving 519 cases for analysis Each of the 519 patients studied fully had a definite histological diagnosis of adenocarcinoma For the purpose of this study carcinoma of the caecum was defined as tumours the margins of which were within 10 cm of the ileocaecal valve Tumours of the right colon and hepatic flexure with a proximal margin further than 10 cm from the ileocaecal valve were not studied. Dukes' classification was as defined in the Large Bowel Cancer Project[4,13]. When no lymph nodes were identified in the resected specimen and there was no evidence of distant spread these tumours were classified as Dukes' B. Local malignant invasion was determined by the surgeon in tumours not resected and from histological examination of resected specimens Local recurrence was defined as convincing evidence of recurrence of cancer in the right side of the abdomen or at the anastomosis, but did not include hepatic or peritoneal secondaries[4]. The median follow-up of these 519 patients was 74 months (range from 9 months to 14 years).

Particular reference was made to a past history of appendicectomy, and further information was obtained from pathological examination of right hemicolectomy specimens. The time between appendicectomy and a diagnosis of carcinoma of the caecum was noted, as was whether the appendicectomy was performed for appendicitis or during the course of another operation An age and sex matched group of 519 patients with no known abdominal pathology, undergoing breast, hernia, and varicose vein surgery was also studied to determine the incidence of previous abdominal operations

Clinicopathological details of the 519 patients with carcinoma of the caecum were analysed to determine differences between those with and without a history of appendicectomy The χ^2 test was used for statistical analysis

The effect of various factors on survival was examined in 458 of 519 patients who were followed up for 2 years The factors assessed were age, sex, previous appendicectomy, emergency or elective presentation, Dukes' classification, tumour differentiation, and local invasion Initially a univariate analysis using the χ^2 test was performed for each factor against the number surviving at 2 years. Subsequently, a multivariate discriminant analysis was performed to identify factors of independent prognostic significance for survival at 2 years The analysis was carried out using the Statistical Package for the Social Sciences–X (SPSS-X, SPSS UK Ltd, Walton-on-Thames, UK) Survival curves to 10 years for patients with and without a history of appendicectomy were constructed by the life table method[14] and include both in-hospital mortality and those cancers discovered at autopsy Age adjustment was performed by comparison with figures for England and Wales from 1980 to 1982[15].

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Results

During the time period studied, 553 patients were found to have a carcinoma of the caecum or ascending colon and their median age was 73 years (range 14–96 years); 55·9 per cent were older than 70 years and 18·5 per cent were older than 80 years. Of these patients 330 (59·7 per cent) were women and 223 (40·3 per cent) were men. Surgery was performed in 518 patients (93·6 per cent), 25 did not have an operation and in ten cases the diagnosis was made at autopsy. Thirty-four patients were excluded because of inadequate past history or histology, or because of incomplete follow-up

Previous operations

Of the 519 patients in whom information was available, 133 (25·6 per cent) had previously undergone an appendicectomy, 43 (8·3 per cent) a cholecystectomy, 22 (4·2 per cent) a 'gastric' operation and 38 (12·3 per cent of 310 women) a hysterectomy. In 24 of the patients who had undergone cholecystectomy and in 20 who had a previous hysterectomy an appendicectomy was performed at the same time. Thus 89 appendicectomies were performed for suspected appendicitis and 44 as a secondary procedure. No information was available on the degree of appendiceal inflammation.

Of the 519 control patients 120 (23·1 per cent) had undergone a previous appendicectomy, an incidence similar to the study group ($\chi^2=2\cdot29$, $P>0\cdot05$). Cholecystectomy had been performed on 30 control patients (5·8 per cent), 53 had undergone a hysterectomy (17·1 per cent of 310 women) and 18 (3·5 per cent) a 'gastric' operation.

Clinicopathological details

The clinical details of patients with and without a history of appendicectomy are shown in *Table 1*. There was no difference in the sex ratio, age, or mode of presentation between the two groups of patients. Patients with a history of appendicectomy had a significantly poorer Dukes' classification (*Table 2*) and also had less well differentiated carcinomas (*Table 3*). There was no relationship between the distance of the caecal carcinoma from the ileocaecal valve (1–10 cm) and the clinicopathological details relating to a history of appendicectomy.

Twenty patients (5·2 per cent) with no history of appendicectomy had synchronous large bowel carcinomas and 74 (19·2 per cent) had adenomas. The corresponding figures for patients who had had appendicectomy were similar, with ten carcinomas (7·5 per cent) and 30 (22·6 per cent) adenomas. Thirteen metachronous carcinomas and ten adenomas have to date been found in patients with no history of appendicectomy. Similarly, two metachronous carcinomas and two adenomas have been found in patients who had previously undergone appendicectomy.

Table 1 *Clinical details in patients with and without a history of appendicectomy*

	No appendicectomy ($n=386$)	Appendicectomy ($n=133$)
Men	160 (41·5)	49 (36·8)
Women	226 (58·5)	84 (63·2)
Median age (years)	73	73
Percentage aged > 70 years	54·2	60·9
Emergency	131 (33·9)	47 (35·3)
Elective	249 (64·5)	84 (63·2)
Autopsy	6 (1·6)	2 (1·5)

Values in parentheses are percentages

Table 2 *Dukes' classification in patients with and without a history of appendicectomy*

Dukes' classification	No appendicectomy ($n=386$)	Appendicectomy ($n=133$)
A	21 (5·4)	5 (3·8)
B	176 (45·6)	33 (24·8)
C	133 (34·5)	57 (42·9)
'D'	56 (14·5)	38 (28·6)

$\chi^2=23\cdot88$, $P<0\cdot001$ (overall appendicectomy *versus* no appendicectomy); values in parentheses are percentages

Table 3 *Tumour differentiation in patients with and without a history of appendicectomy*

Differentiation	No appendicectomy ($n=386$)	Appendicectomy ($n=133$)
Well	80 (20·7)	12 (9·0)
Moderate	210 (54·4)	72 (54·1)
Poor	96 (24·9)	49 (36·8)

$\chi^2=12\cdot72$, $P<0\cdot01$ (overall appendicectomy *versus* no appendicectomy); values in parentheses are percentages

Table 4 *Histology: the relationship of abdominal wall fixity to Dukes' classification*

	Number of fixed tumours		
Dukes' classification	No appendicectomy ($n=386$)	Appendicectomy ($n=133$)	*P* value
A	0/21	0/5	
B	4/176 (2·3)*	12/33 (36)	<0·001
C	8/133 (6·0)	20/57 (35)	<0·001
'D'	10/56 (18)*	21/38 (55)	<0·001

Significance values are for no appendicectomy *versus* appendicectomy. * $P<0\cdot001$ (Dukes' B *versus* 'D'); values in parentheses are percentages

Local invasion into the abdominal wall and muscle was present in 22 (5·7 per cent) of the patients without previous appendicectomy and 13 (59 per cent) of these tumours were resected. In contrast 53 (39·8 per cent) patients who had previously undergone appendicectomy had evidence of local invasion ($\chi^2=93\cdot3$, $P<0\cdot001$) and 36 (68 per cent) were resected. Thus 71 per cent of tumours with local invasion were associated with a history of appendicectomy. It was not possible to determine whether the local invasion was inflammatory or malignant in the 26 unresected cases. The relationship of local invasion to Dukes' classification is shown in *Table 4*. The incidence of local invasion was higher for all Dukes' classifications (except A) in patients who had previously undergone appendicectomy. In patients with no history of appendicectomy the incidence of local invasion increased with Dukes' classification whereas in patients who had previously undergone appendicectomy this relationship was less marked. The number of cases of local invasion into abdominal viscera was similar in the two groups of patients at 29 of 386 (7·5 per cent) and six of 133 (4·5 per cent), respectively.

Histopathology of the appendix

Ten patients with carcinoma of the caecum presented with acute appendicitis and 11 had a mucocele of the appendix. These 21 patients were allotted to the 'no previous appendicectomy' group. Three patients had an appendicectomy within 1 year of the diagnosis of carcinoma of the caecum. The incidence of acute appendicitis as the presenting symptom of carcinoma of the caecum was thus 13 of 386 (3·4 per cent) of patients at risk. In three patients a discharging fistula through an old appendicectomy scar was the first sign of carcinoma of the caecum.

Surgery

Of the patients with no history of appendicectomy, 360 of 386 (93·3 per cent) underwent resection and 26 (6·7 per cent) had either no operation (14, 3·6 per cent) or a palliative procedure

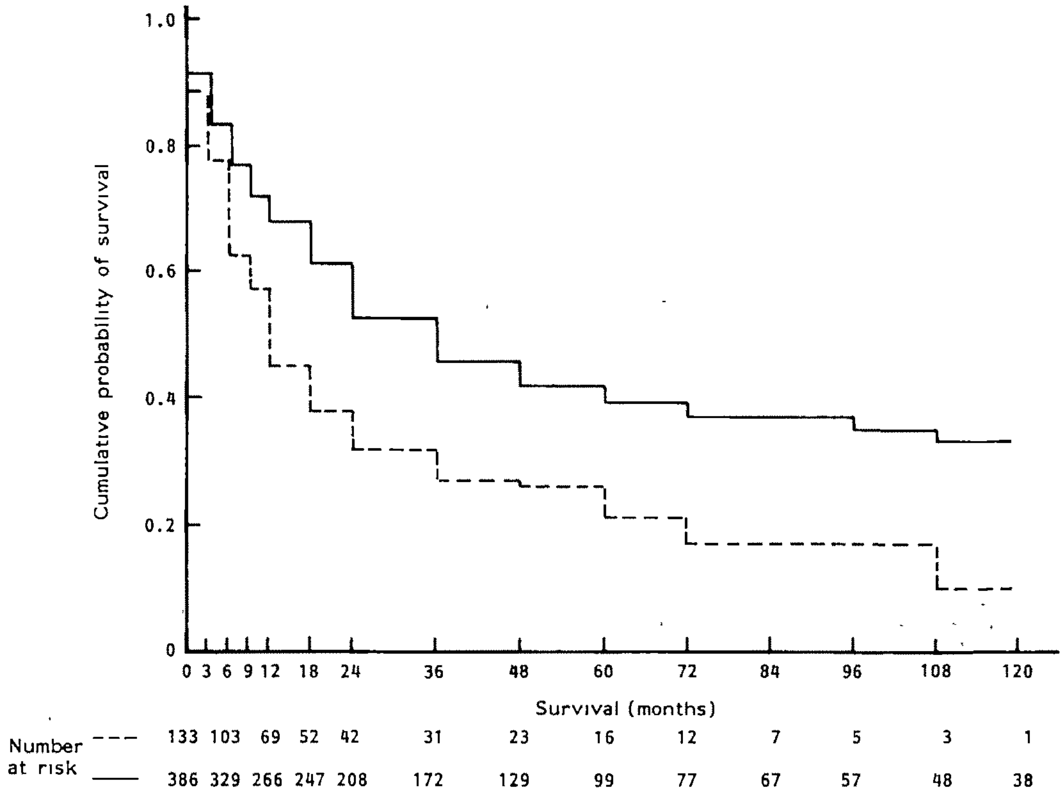

Figure 1 *Survival of patients with and without a history of appendicectomy; ——, no appendicectomy, ---, appendicectomy The number of patients at risk are given*

(12, 3·1 per cent) In contrast only 100 of 133 (75·2 per cent) patients with a history of appendicectomy underwent resection ($\chi^2=32\cdot1$, $P<0\cdot001$) with 33 (24·8 per cent) patients having either no operation (six, 4·5 per cent) or a palliative procedure (27, 20·3 per cent). Overall 59 patients had no resection performed, 32 underwent palliative bypass, eight had laparotomy only, 12 had no operation, and eight tumours were discovered at autopsy; most of these were Dukes' 'D' tumours.

Survival

The overall survival rate of the 519 patients is shown in *Figure 1*, and was significantly less for patients with a history of appendicectomy ($\chi^2=7\cdot75$, $P<0\cdot01$). The 2-year survival rate, based on the 458 patients with 2-year follow-up, for patients with no appendicectomy was 53·7 per cent (182 of 339), and for patients with previous appendicectomy it was 26·1 per cent (31 of 119) ($P<0\cdot001$).

Univariate statistical analysis identified five factors that were significantly related to survival at 2 years. All factors, their incidence, and the relationship to survival are shown in *Table 5*. On performing a discriminant analysis to allow for the inter-relationship of factors, a model involving just four variables resulted In deriving this model a step-wise approach was adopted, with a significance criterion of $P<0\cdot05$ for the inclusion of variables in the model. The variables contained in the final model, in the order of inclusion, were Dukes' classification (P for inclusion $<0\cdot001$), local invasion ($P<0\cdot001$), tumour differentiation ($P<0\cdot001$), and a past history of appendicectomy ($P=0\cdot027$). The above model correctly predicted the outcome (i.e. survival at 2 years) for 79 per cent of cases when it was applied to the whole data set from which the model was derived.

Local recurrence was more commonly observed in patients with a previous appendicectomy and occurred in 18 of 56 (32·1 per cent) and 24 of 183 (13·1 per cent) cases, respectively ($\chi^2=10\cdot72$, $P<0\cdot01$). Local recurrence in an old appendix wound occurred in ten cases. Anastomotic recurrence was seen in 12 cases, 2·6 per cent of right hemicolectomies, and was unrelated to a history of appendicectomy.

Table 5 *Factors related to survival in the univariate analysis*

	Percentage of patients	Percentage of patients alive at 2 years	χ^2 test (P value)
Sex			
Male	41·7	47·1	0·823
Female	58·3	46·1	
Age (years)			
<69	39·3	50·6	0·162
>70	60·7	43·9	
Appendicectomy			
Yes	26·0	26·1	<0·001
No	74·0	53·7	
Presentation			
Emergency	36·0	34·5	<0·001
Elective	64·0	53·2	
Dukes' classification			
A	4·1	84·2	<0·001
B	38·0	79·3	
C	34·9	32·5	
'D'	22·9	6·7	
Differentiation			
Well	16·2	79·7	<0·001
Moderate	53·5	49·4	
Poor	30·3	23·7	
Local invasion			
Yes	23·4	17·8	<0·001
No	76·6	55·3	

Discussion

Colorectal cancer is the second most common malignancy in both men and women in this country with over 38 000 cases and 17 000 deaths being attributable to the disease each year in England and Wales[16]. Carcinomas of the right colon are more common among women, as in this study, in contrast to the rectum where more cases are seen in men[4,5]. A large proportion of patients with right colon cancers are elderly[4,8–10] and we have confirmed this observation, over half our patients being above 70 years of age and nearly one-fifth being older than 80 years.

Although some studies have shown that right-sided colonic cancers are associated with increased[17,18] or decreased[7,19,20] survival compared with other sites in the large bowel, two recent large studies[4,21] found no significant difference in survival for growths throughout the colon and rectum In the Large Bowel Cancer Project[4], however, it was found that tumours of the right colon were more likely to be poorly differentiated and locally advanced in terms of fixation and penetration of the large bowel. In that study a quarter of right colonic cancers were poorly differentiated, 41 per cent were locally fixed, and one-fifth showed evidence of distant metastases. The present study shows similar results with only 5 per cent of tumours being Dukes' A and 14·5 per cent showing evidence of local invasion. Previous authors[8–12,22,23] with smaller numbers of patients, have also commented on the high incidence of local fixity of cancers of the caecum and ascending colon but none has yet investigated the possible relationship between this fixity and previous surgery.

A history of appendicectomy is common and this operation had been performed in over a fifth of our control group of patients. Previous studies have documented appendicectomy rates of 17·5 per cent for men and 33·3 per cent for women in New York[24], and 19·0 per cent for men and 13·0 per cent for women in the UK[25]. These and other studies[26,27] found no relationship between appendicectomy and the later development of colonic cancer and we have confirmed this in the present study. It is of interest that equal numbers of synchronous and metachronous carcinomas and adenomas were seen in patients with and without a history of appendicectomy.

Carcinoma of the caecum rarely presents as acute appendicitis[9–11,28] and we found this mode of presentation in 3·4 per cent of susceptible cases. The possibility of carcinoma of the right colon must be considered in all patients with appendicitis over the age of 50 years, as three of our patients had an appendicectomy within 1 year before carcinoma of the caecum was diagnosed. Three patients also presented with a discharging fistula through an old appendix scar and this confirms the observation of El-Domeiri and Whiteley[12] who found fistulation only when the integrity of the abdominal wall and parietes had been compromised by previous surgery.

In this study a history of appendicectomy was associated with a significantly increased chance of local fixity and invasion of the abdominal wall, and it is noteworthy that over 70 per cent of cancers invading the abdominal wall were associated with previous appendicectomy. Most tumours invading the abdominal wall were resected *en bloc*, and the survival of such patients was then related to the histological stage and grade of the tumour. This confirms previous observations that locally invasive carcinomas of the colon can be resected with good long term results[12,29] The presence of local fixity and invasion of the abdominal wall may relate to adhesions after appendicectomy with scar tissue in the caecal wall, and to the inflammatory changes of appendicitis itself. Unfortunately as many appendicectomies were performed decades earlier we are unable to comment further on this.

It is of interest that patients with a past history of appendicectomy had more advanced and less well differentiated tumours, although it must be emphasised that in a retrospective study there is considerable observer variation among pathologists in relation to histological grading[30]. These factors plus the increased incidence of local fixity led to a significant reduction in resection rates after appendicectomy, although in both groups of patients most of the tumours were resected. The reason for tumours being more advanced after previous appendicectomy may relate to delayed presentation with difficulty in examination due to scar tissue. There was, however, no difference in the number of patients presenting as an emergency nor in the symptoms at presentation between the two groups of patients. Local adhesion formation may be conducive to greater local tumour spread, raising the possibility that an intact serosal surface may provide some barrier to local tumour spread Previous surgery in the form of appendicectomy might also be associated with adaptive hyperplasia[31,32] of the epithelium in the caecum and this could possibly lead to altered growth characteristics in the carcinoma itself. In addition, it is interesting to speculate that the loss of lymphoid tissue in the appendix could alter the immune response to local carcinomas in the caecum.

The survival of patients with carcinoma of the caecum who had previously undergone appendicectomy was significantly lower than those patients with no such operative history. Univariate analysis identified five highly significant factors relating to survival at 2 years. Multivariate analysis demonstrated that four of these factors were of independent prognostic significance for survival. The most important were the well recognized factors of Dukes' classification, tumour differentiation, and local invasion[33,34]. However, this study also identified that previous appendicectomy contributed significantly as an independent risk factor for survival. It is also noteworthy that age in itself was not a significant risk factor, confirming recent reports[35].

There was also a significant increase in the incidence of local recurrence after previous appendicectomy and this was often in the appendix scar itself. This might relate to the presence of more aggressive carcinomas or to incomplete tumour clearance at operation because of scar tissue and adhesions. A case may be made for removal of the old appendix scar with the carcinoma in patients undergoing curative surgery and this observation might therefore lead surgeons to resect areas of bowel adhesion widely when they are in the vicinity of a primary tumour. Anastomotic recurrence was low in this study at 2·6 per cent and this confirms the earlier study of Wright *et al.*[36] who reported tumour recurrence in 0·7 per cent of ileocolic anastomoses compared with 12 per cent of colocolic anastomoses. As recently emphasised by Umpleby and Williamson[32], however, this low incidence of ileocolic recurrence may relate to the relative difficulty in diagnosing an ileocolic anastomotic tumour before it presents as a massive local recurrence.

The present study has demonstrated for the first time that previous appendicectomy has an independent influence on outcome and significantly decreases survival in patients who subsequently develop a carcinoma of the caecum. The reason for this is unclear but may relate to delayed presentation, altered growth characteristics, or postoperative adhesions with scar tissue. A prospective study is needed to evaluate more fully the possible detrimental effect of previous appendicectomy on both cancer of the caecum and cancer throughout the large bowel.

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Critical assessment of the quality of continence after postanal repair for faecal incontinence

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One hundred and twenty-four patients had a postanal repair for the treatment of faecal incontinence between January 1976 and July 1987. One hundred and sixteen of these patients have been followed up for more than 1 year with a median follow-up of 5 years. Incontinence was improved in 81 per cent of patients. Furthermore, bowel frequency fell: 58 per cent had more than four bowel movements before operation compared with 19 per cent after operation. However, 60 per cent of patients still claimed urgency, 76 per cent still leaked faeces and 52 per cent continued to wear pads after the operation. Maximum resting anal pressure and maximum squeeze pressure did not change significantly after operation either in patients whose bowel control was improved or in those who were not. The results indicate that the quality of continence after postanal repair is poor.

Keywords: Maximum resting anal pressure, maximum squeeze pressure, bowel frequency

Faecal incontinence is physically and emotionally disabling. Although all age groups may be affected, it is rare before the third decade, but increases thereafter. The majority of patients with faecal incontinence have evidence of nerve damage to the pelvic floor and/or external sphincter[1]. Many of these patients also have a history of obstetric trauma:prolonged labour, forceps delivery or third degree tears[2]. Other patients develop incontinence secondary to chronic straining, rectal prolapse, iatrogenic damage, particularly after anal dilatation or fistula operation, and some have neurological disorders or congenital anomalies[3]. Incontinence may also occur secondary to faecal impaction or after sphincter-saving operations[4].

The aim of postanal repair is to restore the anorectal angle[5] and the flap valve of the puborectalis[6]. Early functional results of postanal repair reported from St. Mark's Hospital, London, UK, and this unit have been encouraging[7], but in these studies follow-up has been short and many surgeons express the view that long-term results are disappointing. We have a large series of patients operated on by one surgeon over 11 years where long-term follow-up is now available. Results have been assessed objectively by an independent observer using a specific questionnaire and physiological monitoring.

Patients and methods

Between January 1976 and July 1987, 124 patients with faecal incontinence underwent a postanal repair Incontinent patients were selected for operation if they had low resting and squeeze pressures, no rectal prolapse, a normal sphincter ring with a normal perineal body, and electromyographic evidence of pelvic floor neuropathy with poor recruitment during attempted pelvic floor contraction together with an obtuse anorectal angle during videoproctography.

Symptoms and clinical findings were recorded on specific follow-up data sheets. Preoperative and postoperative anal canal pressures were studied in 68 patients. All patients were reviewed to assess the functional results and quality of continence at 12 months after operation and annually thereafter.

Anal canal pressures were measured in the left lateral position after rectal examination using a closed water-filled balloon probe attached to a transducer and pen recorder Measurements of resting and squeeze pressures were performed at 1-cm intervals 1–5 cm from the anal verge. Maximum basal and squeeze pressures were taken as the highest resting pressure in the anal canal and the highest pressures recorded after voluntary contraction respectively.

Operative procedure

Postanal repair was performed using the intersphincteric approach described by Parks[8]. However, a number of adaptations were made which have already been described[7] These departures from Parks' original operation include avoidance of a weak adrenaline solution, use of a transverse incision, raising a thicker anterior skin flap and mass closure of the pelvic floor with interrupted Dexon® (Davis and Geck, Gosport, UK). The ileococcygeus, ischiococcygeus and pubococcygeus were co-opted in the midline posteriorly after removing the anterior retractor. If there was any rectal damage, contamination or anterior skin flap ischaemia, the wound was left open and the necrotic skin was excised.

Although there were a wide variety of disorders and pathophysiological abnormalities associated with incontinence, all of the patients in this survey were offered postanal repair because there was clinical, electromyographic or videoprotographic evidence of a weak pelvic floor and a deficient puborectalis sling. Although patients with a history of obstetric trauma and previous operations on the anal canal were offered repair they all had physiological or radiographic evidence of a pelvic floor abnormality and an obtuse anorectal angle.

Results

The median age of the 124 patients was 59 years (range 20–84 years). Thirteen patients (10 per cent) were men and 111 (90 per cent) were women.

The aetiology and associated disorders are shown in *Table 1*. Twenty patients had had a full-thickness rectal prolapse; although a previous rectopexy had successfully controlled the prolapse these patients remained incontinent. Idiopathic faecal incontinence was found in 61 patients, only two of whom were men. Of the 59 women, 30 gave a history of prolonged labour or forceps delivery. Twenty-one women had sustained severe obstetric trauma with electromyographic and proctographic evidence of a pelvic floor neuropathy. Thirteen patients had had previous anal surgery and four had had other operations (*Table 1*) but all had evidence of pelvic floor damage.

Thirty-nine patients (31 per cent) had undergone previous treatment for faecal incontinence (*Table 2*).

Of 124 patients having postanal repair, 18 patients (15 per cent) developed a complication (*Table 3*). One obese diabetic patient died 7 days after the operation from a massive pulmonary embolus. Seven patients developed wound sepsis and ten further patients developed ischaemic necrosis in the anterior skin flap. A fistula from the rectum to the incision

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occurred in three patients as a result of iatrogenic damage; these patients have all been successfully managed by repair after raising a proximal colostomy. In three other cases iatrogenic damage was not accompanied by a fistula. Three patients developed a large wound haematoma and one further patient was returned to theatre because of bleeding.

Functional results and quality of continence has been assessed in 116 patients who have been followed-up for between 1 and 10 years. The results were not assessed in eight patients because five patients had had their operation within 3 months of this review, one patient died and two have been lost to follow-up. Ninety-four patients (81 per cent) stated that the degree of continence was definitely improved after the operation, 12 (10 per cent) patients said that improvement had only been minor and 10 said they were no better or worse and all 10 have now had a colostomy (*Table 4*). In the 94 patients who achieved a definite improvement in continence, 61 per cent did so within 3 months of the operation; it took a further 3–6 months in 18 per cent, 6–12 months in 15 per cent, and in 6 per cent of the patients continence was only achieved after 1 year.

Bowel frequency was compared before and after operation (*Figure 1*). Sixty-seven patients (58 per cent) opened their bowels more than four times a day before the operation, compared with only 22 patients (19 per cent) after operation. Although bowel frequency was reduced after operation, eight patients opened their bowels more than six times a day even after the operation and all had persistent and troublesome incontinence

Quality of continence was assessed by asking patients about urgency, leakage of faeces, soiling of pads and ability to discriminate between flatus and faeces (*Figure 2*). Eighty-nine per cent of the patients claimed urgency before operation and 60 per cent still had urgency after operation. Ninety-three per cent experienced involuntary leakage of faeces at least once a month preoperatively and this persisted after operation in 76 per cent Eighty-four per cent of patients soiled pads before operation, and 52 per cent continued to wear pads because of soiling after operation. Forty-five patients (39 per cent) had been unable to discriminate between flatus and faeces before operation, compared with 29 patients (25 per cent) after operation. When results were analysed according to the aetiology of incontinence, patients who had had a previous rectopexy had significantly worse results than all other groups. Only 44 per cent were improved by postanal repair after a previous rectopexy compared with 89 per cent of those with idiopathic incontinence ($P<0.05$). All patients needed to wear a pad

Table 1 *Aetiology and associated diseases*

Rectal prolapse (previous rectopexy successfully controlled prolapse)	20
Idiopathic (30 had prolonged labour)	61
Obstetric trauma	21
Previous anal surgery	
Anal dilatation	6
Haemorrhoidectomy	4
Fistula *in ano*	2
Imperforate anus	1
Other previous operations	
Hysterectomy	1
Jejunoileal bypass	1
Partial colectomy	1
Presacral neurectomy	1
Neurological disorders	
Diabetes	2
Disseminated sclerosis	1
Von Recklinghausen's disease	1
Trauma to perineum	1
Total	124

Table 2 *Previous treatment for incontinence*

Rectopexy	20
Electrical device	13
Thiersch operation	3
Sphincter repair	2
Postanal repair	1
Total	39

Table 3 *Complications*

Ischaemic anterior skin flap	10
Wound infection	7
Fistula	3
Haematoma	3
Diarrhoea (pseudomembranous colitis)	2
Bleeding	1
Death	1
Total	27

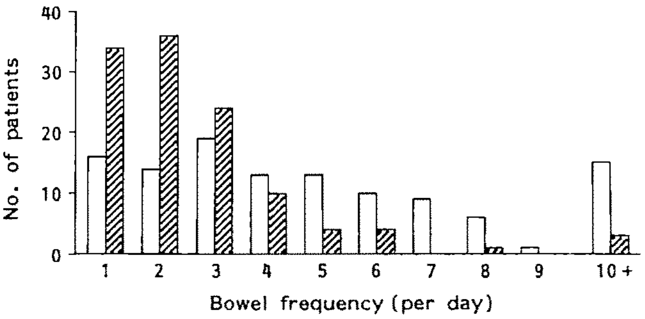

Figure 1 *Bowel frequency before and after operation* □, *before operation,* ■, *after operation*

Table 4 *Faecal continence after postanal repair*

Aetiology and associated diseases	Number	Evaluable	Better	Minor improvement	No better or worse	Urgency	Leakage	Wearing pad	Failure of discrimination
Previous rectopexy	20	18	8 (44)*‡	6	4	10 (55)	16 (89)	18 (100)†	16 (89)
Idiopathic incontinence	61	58	52 (90)	4	2	33 (57)	44 (76)	22 (38)	36 (62)
Obstetric trauma	21	20	17 (85)	2	1	12 (60)	13 (65)	6 (30)	16 (80)
Previous anal surgery	13	11	9 (82)	0	2	7 (64)	9 (82)	7 (64)	10 (91)
Others	9	9	8 (89)	0	1	8 (89)	6 (67)	7 (78)	9 (100)
Total	124	116	94 (81)	12	10	70 (60)	88 (76)	60 (52)	87 (75)

Percentages are given in parentheses * $P<0.05$, compared with idiopathic incontinence, † $P<0.01$, compared with idiopathic incontinence; ‡ $P<0.05$, compared with obstetric trauma

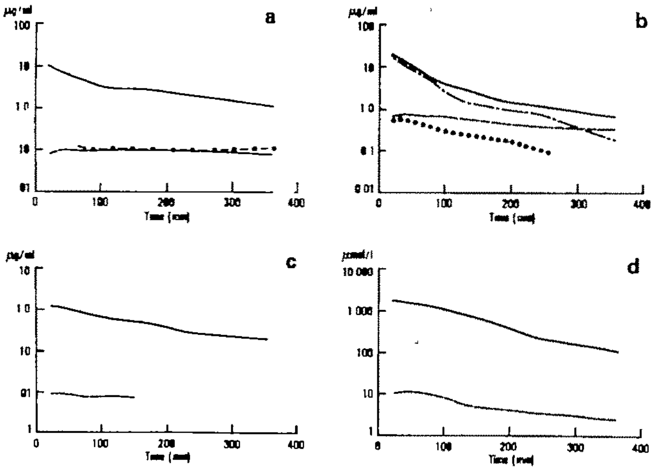

Figure 2 *Quality of continence*

Table 5 *Anal canal pressures before and after operation*

		Pressure (cmH$_2$O)	
	Numbers	Before operation	After operation
Maximum anal pressure			
Total	68	50 (0–140)	51 (13–150)
Improved	50	50 (0–140)	51 (13–100)
Not improved	18	55 (30–124)	53 (20–136)
Maximum squeeze pressure			
Total	68	115 (32–300)	107 (26–336)
Improved	50	106 (32–300)	110 (40–285)
Not improved	18	124 (45–231)	93 (26–336)

Values given are median (range)

because of soiling when postanal repair was used for persistent incontinence after rectopexy compared with 38 per cent of those with idiopathic incontinence ($P<0{\cdot}01$) and 30 per cent of those who had sustained third-degree tears ($P<0{\cdot}05$). There was no apparent difference in the incidence of improved results, urgency, leakage or the use of pads when the group with idiopathic faecal incontinence was compared with those who had sustained obstetric trauma.

Anal canal pressures were measured before operation in almost all subjects but postoperative manometry was only repeated in 68 patients; of these, 50 patients stated that incontinence was improved after the operation and 18 that it was not (*Table 5*). Maximum anal and maximum squeeze pressures did not change significantly after the operation overall or in either subgroup.

Discussion

In order to assess the functional results of postanal repair we analysed several aspects of continence such as bowel frequency, urgency, leakage of faeces, soiling of pads and ability to discriminate between gas and stool. The results were disappointing. 60 per cent of the patients continued to complain of urgency, 76 per cent experienced involuntary faecal leakage and 52 per cent of the patients found that they continued to soil pads after the operation. Despite this, 81 per cent of the patients claimed that bowel control was improved. These paradoxical results might be explained by the fact that the patients seemed to feel that bowel control was better even if the degree of urgency or faecal leakage was only slightly improved. These results indicate that although postanal repair is usually able to improve the degree of faecal incontinence, the quality of continence is poor. Critical evaluation by an unbiased observer probably explains why results from this report appear to be inferior to those previously published from this unit. These results do not suggest that continence deteriorates with time; indeed, in some patients, continence was only restored a year after postanal repair.

Functional results did not correlate with maximum resting pressure or maximum squeeze pressures. Parks believed that the factor most reliably associated with good results was the ability to restore the anorectal angle[9]. Hence, the operation would not have been expected to cause a rise in anal pressure. Indeed, early repeated measurement of anal canal pressures in this unit showed no significant change after postanal repair[10], though later studies suggested that postanal repair resulted in a significant rise in maximum resting pressures[7]. Browning *et al.*[11] observed a significant increase both in maximum resting and squeeze pressures. The most likely explanation for these changes is that the repair also plicates the posterior fibres of the external sphincter.

Thirty-nine patients (31 per cent) had had previous treatment for incontinence. Twenty patients had persistent incontinence despite an earlier rectopexy for rectal prolapse In ten of the 20 patients in this group, results of postanal repair were disappointing and only eight claimed any functional improvement following the operation. Results were significantly worse than in patients with idiopathic faecal incontinence. As a result of these observations, postanal repair for persistent incontinence after rectopexy is rarely advised; furthermore, a combined postanal repair and abdominal rectopexy is not recommended as it is difficult to predict those patients who will remain incontinent. There is also an increased risk of perineal infection if the operations are performed synchronously. Thirteen patients previously had treatment using an electrical device but functional improvement was minimal[12].

This study can be criticized for including 21 patients with obstetric injury, but all had electromyographic evidence of a pelvic floor neuropathy and an obtuse anorectal angle on videoproctography Furthermore, results in these patients did not differ from those with idiopathic faecal incontinence. We believe that in many patients with a history of obstetric trauma, incontinence is more commonly due to a weak pelvic floor rather than a defect in the sphincter ring. Indeed, disruption of the sphincter ring is treated by sphincter repair[7]; despite this practice, unpublished long-term results from this unit suggest that persistent incontinence may occur after this procedure because of an underlying pelvic floor abnormality.

The main factors associated with failure of postanal repair are severe muscle degeneration, the irritable colon syndrome and sepsis at the operation site[13,14]. Severe muscle degeneration may be identified preoperatively by measurement of mean fibre density and a hyperactive sigmoid colon can be identified using preoperative sigmoid manometry. Results in this series were poor if diarrhoea persisted after operation. Unfortunately, the diarrhoea associated with persistent faecal incontinence is usually unpredictable and episodic and therefore is not amenable to treatment with agents such as loperamide or codeine. Patients should also be told to stop straining postoperatively because in some patients progressive pelvic floor neuropathy is encouraged. A stimulant suppository may help some of these patients. Pelvic floor exercises, anal hygiene and attention to bowel habit should also be encouraged in patients who have an imperfect result. Many individuals find that these measures help to achieve a degree of continence that is certainly preferable to a stoma. Sepsis should now no longer be a risk factor, particularly if contaminated wounds are left open; using this policy only seven patients developed wound sepsis after the operation (6 per cent). Conversely, damage to the rectum resulting in an iatrogenic fistula is generally attended by poor results. If the rectum is inadvertently injured at the time of repair, the defect should be sutured as an intra-anal procedure using a Parks' retractor; this policy has been successful in three recent injuries and a covering stoma was not necessary.

Although the quality of continence reported in this critical assessment of postanal repair is far from perfect, almost without exception the patients are grateful for the improvement that has been achieved. Furthermore, they consider their quality of life is infinitely better than having to face the prospect of a permanent stoma.

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Anterior sphincter plication and levatorplasty in the treatment of faecal incontinence

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The surgical treatment of faecal incontinence has been traditionally divided into sphincteroplasty for sphincter disruption and postanal repair for idiopathic cases. However, many studies have failed to show a correlation between outcome and change in the anorectal angle. This study was carried out to determine the effectiveness of anterior sphincteroplasty and levatorplasty in the treatment of faecal incontinence, regardless of aetiology. Thirty consecutive patients underwent surgery, 14 with traumatic sphincter injuries and 16 with idiopathic faecal incontinence. A satisfactory clinical result was obtained in ten (71 per cent) patients in the traumatic group and in ten (62 per cent) in the idiopathic group. This was associated with a significant increase in maximum voluntary contraction pressure in the traumatic group and in those patients who had a good result in the idiopathic group (traumatic: preoperative median 80 cmH$_2$O (range 50–115 cmH$_2$O) versus *postoperative 115 cmH$_2$O (75–290 cmH$_2$O),* $P<0{\cdot}005$; *idiopathic: preoperative 105 cmH$_2$O (45–190 cmH$_2$O)* versus *postoperative 120 cmH$_2$O (45–230 cmH$_2$O),* $P<0{\cdot}05$; *Wilcoxon paired signed ranks test). There was also a significant improvement in anal sensation in the upper anal canal in both groups (traumatic: preoperative mean 17 mA* versus *postoperative 11 mA,* $P<0{\cdot}05$; *idiopathic: preoperative 24 mA* versus *postoperative 9 mA,* $P<0{\cdot}02$). *The anorectal angle increased in the idiopathic group at rest (preoperative median 105° (range 86–152°)* versus *postoperative 118° (95–180°),* $P<0{\cdot}05$). *In conclusion, the type of approach (anterior or posterior) and the anorectal angle are irrelevant to the outcome of surgery for idiopathic faecal incontinence. Success appears to be related more to improved sphincter pressure and anal sensation.*

Keywords: Anterior sphincter repair, incontinence, levatorplasty

It has been suggested that the acute anorectal angle produced by the action of the puborectalis muscle is fundamental to the maintenance of continence by creating a flap-valve effect[1,2]. Many investigators have described an obtuse anorectal angle in patients with idiopathic faecal incontinence[1,3–5]. The operation of postanal repair was devised to recreate the acute angle and thereby improve continence[2].

However, some patients with idiopathic faecal incontinence do not have an obtuse anorectal angle[6,7] and the pressure changes during a Valsalva manoeuvre suggest that continence is maintained by sphincteric action rather than a flap-valve effect[8]. Furthermore it has been demonstrated by proctographic techniques that the anterior rectal wall is not in contact with the upper anal canal during periods of high intra-abdominal pressure[9,10].

These findings have led us to modify our approach to the management of incontinence. In the past we have subdivided patients on the basis of clinical, physiological and electromyographic findings into two main groups: those with traumatic sphincter disruption (usually secondary to obstetric injury) and those with idiopathic faecal incontinence. The former were offered anterior sphincter plication[11] and the latter postanal repair[12].

From 1987 onwards we have used an anterior approach to treat all patients with incontinence, irrespective of the aetiology. In this paper we describe the outcome of patients treated by such an approach. A detailed clinical and physiological assessment was made before and after surgery in an attempt to determine those factors responsible for improved continence.

Patients and methods

From January 1987 to November 1988, 38 patients have had anterior sphincter surgery at the Bristol Royal Infirmary. Thirty patients have had complete preoperative and postoperative investigations and are reported here. Fourteen patients had an anterior sphincter tear demonstrated by electromyography (EMG) or at operation, and in 16 no sphincter injury could be demonstrated and these patients were therefore classified as having idiopathic faecal incontinence. Clinical details are given in *Table 1*

Clinical assessment

All patients had a thorough clinical examination including examination of the lumbosacral plexus, digital rectal examination, sigmoidoscopy and proctoscopy. The degree of incontinence was assessed and graded as described by Browning and Parks[13]: Grade A, continent to solids and liquids and also to flatus; Grade B, continent to solid and usually liquid but incontinent to flatus; Grade C, partial return of function with generally acceptable continence for solid stool but no control over liquid or flatus; and Grade D, continued faecal leakage. Patients with

Table 1 *Clinical details of patients*

	Anterior sphincter tear ($n=14$)	Idiopathic faecal incontinence ($n=16$)
Age (years)	32 (23–49)	66 (36–80)
Parity	2 (0–3)	2 (0–7)
Follow-up duration (months)	5 (1–18)	4 (2–12)

Values are median (range)

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Grade A or B were defined as having a successful result, and those with Grades C and D as failures.

Operative technique

Surgery, after preparation with Picolax® (Nordic Pharmaceuticals Ltd., Feltham, UK), was performed by one surgeon (D.C.C.B.). Prophylactic antibiotics were also used: three perioperative doses of cefuroxime (750 mg) and metronidazole (500 mg). The technique of sphincter plication for patients with an obstetric sphincter injury was based on that described by Parks and McPartlin[11]. In addition, however, the levator space was entered and these muscles were plicated between the rectum and vagina using two superficial and two deep 2/0 Prolene® (Ethicon Ltd., Edinburgh, UK) sutures. This was performed in an attempt to lengthen the anal canal and augment the perineal body. Through an anterior incision the cut and retracted ends of the sphincter were separated from the internal sphincter, which was plicated with 2/0 Vicryl® (Ethicon Ltd.). The ends of the external sphincter were then overlapped and sutured with interrupted 2/0 Prolene.

In patients with idiopathic faecal incontinence the sphincters were exposed anteriorly using the intersphincteric plane to gain access to the levator muscles. The levators were plicated with interrupted 2/0 Prolene. The external sphincter was then divided in the midline anteriorly and plicated in the same way as for traumatic disruption. The internal sphincter was plicated as described above.

Primary closure after this repair results in excessive tension. The wounds were therefore only partially closed with the small remaining defect left to heal by secondary intention. This invariably occurred within 4–6 weeks. Covering stomas were not used.

Manometry

The manometric system consisted of a water-filled balloon, 6 mm in diameter, connected via non-distensible tubing to a Statham transducer (P23Gb, Spectromed, Coventry, UK). Using a station pull-through technique the sphincter length, maximum resting pressure and maximum voluntary contraction pressure were measured. This technique has been described in detail previously[14]

Anal sensation

Anal mucosal electrosensitivity was measured in the lower, middle and upper thirds of the anal canal as defined by manometry. A catheter carrying two platinum electrodes 1 cm apart was inserted into the anal canal and a small electric current from a constant current generator (Department of Medical Physics, Bristol Royal Infirmary, Bristol, UK) was passed across the electrodes[15]. The threshold to this stimulus was determined three times and the mean value recorded.

Electromyography

In eight of the 14 patients with a history of obstetric trauma a gap in the sphincter was demonstrated preoperatively using a Medelec EMG recorder (Type MES, Medelec, Woking, UK) and a conventional concentric needle (Type 13L49, Dantec, Copenhagen, Denmark). In the remaining six patients the sphincter defect was found at operation.

Proctography

The patient was placed in the left lateral position and 50 ml of a semisolid mixture of barium sulphate and potato starch was injected into the rectum. The anal canal was outlined by a string of metal beads connected to a wooden ball placed in the rectum. The anorectal angle was defined as the angle between the central axis of the rectum and the anal canal as shown by the beads. The degree of perineal descent was measured from the highest bead in the anal canal and the plane of the perineum. This represents the line connecting the anterior portion of the symphysis pubis with the lowermost part of the coccyx. Lateral radiographs were taken in the positions of rest, maximum sphincter contraction (squeeze) and/or bearing down as if at stool (strain).

Table 2 *The number of patients undergoing surgery and the outcome in the traumatic and idiopathic groups*

	Traumatic		Idiopathic	
Grade	Preoperative	Postoperative	Preoperative	Postoperative
A	0	7	0	5
B	0	3	0	5
C	7	3	6	3
D	7	1	10	3

Grade A, continent to solids, liquids and flatus; Grade B, continent to solid and liquid, incontinent to flatus; Grade C, continent to solids, Grade D, continued faecal leakage

Statistical analysis

The Mann–Whitney *U* test was used to compare individual groups. The Wilcoxon paired signed ranks test was used to compare preoperative and postoperative results in the same patients. Results are quoted as medians with ranges in parentheses, unless otherwise stated.

Results

Clinical

Ten of the 14 patients in the traumatic group (71 per cent) had a successful result, their continence being either Grade A or B after operation. In those patients who had idiopathic faecal incontinence, ten of 16 were successful (62 per cent; *Table 2*).

Manometry

There was no significant change in sphincter length or maximum resting pressure following surgery in either group. Surgery improved the maximum voluntary contraction pressure in the traumatic group (preoperative median 80 cmH_2O (range 50–115 cmH_2O) *versus* postoperative 115 cmH_2O (75–290 cmH_2O), $P<0{\cdot}005$) but had no significant effect on maximum voluntary contraction in the idiopathic group as a whole (preoperative 107 cmH_2O (5–200 cmH_2O) *versus* postoperative 117 cmH_2O(45–230 cmH_2O), n.s.; *Table 3*). However the subgroup of ten idiopathic patients who had a successful result maximum voluntary contraction did improve significantly (preoperative 105 cmH_2O (45–190 cmH_2O) *versus* postoperative 120 cmH_2O (45–230 cmH_2O), $P<0{\cdot}05$). This was not true for resting pressures. However, it is interesting that taking all the patients together, those who had a good result clinically had a significantly higher preoperative resting pressure than those who were failures (60 cmH_2O (10–105 cmH_2O) *versus* 40 cmH_2O(0–74 cmH_2O, $P<0{\cdot}05$, Mann–Whitney *U* test).

Mucosal electrosensitivity

In the lower and midzones of the anal canal there was no change in sensitivity following surgery (*Table 3*). In the upper zone however there was a marked improvement in sensation in both the traumatic group (preoperative mean 17 mA *versus* postoperative 11 mA, $P<0{\cdot}05$) and the idiopathic group (preoperative 24 mA *versus* postoperative 9 mA, $P<0{\cdot}02$)

Radiology

There was an increase in anorectal angle at rest in the idiopathic group (preoperative median 105° (range 86–152°) *versus* postoperative 118° (95–180°), $P<0{\cdot}05$). The only other changes were in the traumatic group where the angle was more acute on squeeze and straining after operation (*Table 3*).

There was no change in the degree of perineal descent in either group.

Discussion

The operation of postanal repair stemmed from the flap-valve theory of continence but the evidence against this concept is now overwhelming. Firstly, a significant number of patients with idiopathic faecal incontinence do not have an obtuse anorectal angle[6,7]. Secondly, if the theory were correct one would expect a high pressure zone just above the anal canal during a Valsalva manoeuvre and Read[8] has demonstrated that this is not the case. He suggested that the high pressure zone in the anal canal was of primary importance. Furthermore, proctographic studies have failed to demonstrate the mechanism[9]; indeed the reverse is the case. Using videoproctography with additional sphincter EMG and anorectal pressure monitoring Bartolo *et al.* demonstrated that the anterior rectal wall does not occlude the anal canal during rises in intra-abdominal pressure[10]; continence under these circumstances was maintained principally by sphincteric action.

The findings of the current study support the view that the sphincters act by creating a high pressure zone in the anal canal.

Table 3 *The results of surgery in the traumatic and idiopathic groups as defined by the changes in physiological and radiological parameters*

	Traumatic		Idiopathic	
	Preoperative	Postoperative	Preoperative	Postoperative
Sphincter length (cm)	3 (2–4	3 (1–3·5)	3 (0–4)	3 (2–4)
Maximum resting pressure ($\mathrm{cmH_2O}$)	55·4 (28–105)	62 (33–80)	55·5 (0–100)	56 (30–137)
Maximum voluntary contraction pressure ($\mathrm{cmH_2O}$)	80 (50–115)	†115 (75–290)	107 (5–200)	117 (45–230)
Mucosal electrosensitivity (mA)				
Lower anal canal	6·3 (4·3–17·6)	8 (4–11)	7 (4–16·6)	8 (4–25)
Middle anal canal	6·8 (4–20)	6·3 (3–19)	9 (3–25)	8 (3–25)
Upper anal canal	17 (4–25)	*11 (2–25)	24 (3–25)	*9 (6–25)
Anorectal angle (°)				
Rest	107 (83–134)	98 (83–117)	105 (86–152)	118 (95–180)*
Squeeze	100 (84–134)	*91 (60–112)	97 (71–153)	113 (85–163)
Strain	119 (108–135)	*110 (90–136)	123 (89–152)	125 (101–180)
Perineal descent (cm)				
Rest	−0·7 (−2·6 to 0·2)	−1·0 (−2·7 to 0·9)	−2·1 (−3·2 to 0)	−2·4 (−3·4 to 0)
Squeeze	−0·3 (−2·2 to 0·8)	−0·4 (−2·1 to 0·9)	−1·6 (−3·2 to 0·6)	−1·7 (−2·7 to 0·8)
Strain	−2·2 (−5·7 to −0·1)	−3 (−6·3 to 0)	−3·5 (−8·2 to −1·2)	−4·2 (−7 to 0)

Values are median (range); * $P<0·05$, † $P<0·005$ (Wilcoxon paired signed ranks test)

Surgery was designed to improve the function of the external sphincter and this was achieved in the traumatic group and in those patients with idiopathic incontinence who had a successful result. We were not able however to demonstrate an increase in the length of the functioning sphincter, a factor which has been associated with successful postanal repair[6].

Keighley and Fielding[16] have also described an improvement in voluntary contraction pressures following sphincter repair for traumatic disruption. There is, however, a considerable divergence of opinion regarding the effect of postanal repair on anal sphincter pressures. Browning and Parks[13] described an increase in voluntary pressures but others have shown a rise in resting pressure alone[16] or no change in either component[6].

In this series, surgery for incontinence resulted in improved sensation in the upper zone of the anal canal. We have previously described a similar improvement in upper anal canal sensation following postanal repair[7] but others have found no change[17]. Any reduction in sensory thresholds is probably due to lax or prolapsed anal mucosa being drawn back up into the anal canal by the plication of the levators and external sphincter.

Awareness of the presence and nature of rectal contents is an important factor in maintaining normal continence and therefore this improved sensation may well contribute to the success of surgery.

The clinical outcome for traumatic sphincter injury in this study is similar to that reported by others[18–20]. With an anterior approach in the idiopathic group we have achieved a satisfactory outcome in 62 per cent despite the anorectal angle becoming more obtuse at rest. This degree of success is nearly identical to that of postanal repair on our unit (59 per cent) as well as that reported by others[7,16,21].

In the traumatic group the anorectal angle did become more acute both on squeezing and straining but not at rest. However, these are not the patients in whom an obtuse angle is cited as a cause of incontinence. They had a clearly defined breach in the external sphincter and the changes in anorectal angle probably reflect the improved action of the levators following their plication. Also, it is difficult to see how such a small change in angle (9°) could affect continence.

In conclusion, it appears that the type of approach (anterior or posterior) and the anorectal angle are irrelevant to the outcome of surgery for idiopathic faecal incontinence. Success is more related to improved sphincter pressures and anal sensation The anterior approach has the advantage that preoperative EMG to demonstrate a sphincter defect is not necessary.

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Declining indications for abdominoperineal resection

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In 126 consecutive patients operated on for carcinoma of the lower two-thirds of the rectum, a consistent policy of sphincter preservation resulted in 100 (79 per cent) having anterior resection and 22 (17 per cent) abdominoperineal resection. Perioperative complications in the anterior resection group were: death (two patients), clinical leakage (three patients), pulmonary embolism (five patients), pelvic haematoma (one patient), small bowel obstruction (one patient) and wound sepsis (six patients). Of 55 patients who had a potentially curative anterior resection with follow-up of at least 2 years, one developed local recurrence. Five per cent of patients had significant continence problems. Low anterior resection for carcinoma is associated with low perioperative morbidity, satisfactory functional results and acceptable local recurrence rates.

Keywords: Rectal carcinoma, anterior resection morbidity, neorectal function, local recurrence

In the surgery of rectal cancer the emphasis has moved from abdominoperineal excision to anterior resection. The change, however, outside specialized units[1,2] has been slow, reluctant and sometimes controversial[3]. To justify the increased frequency of anterior resection it must be shown that: the difficult problems of anastomotic dehiscence and pelvic sepsis[4,5] can be overcome, closer longitudinal margins of resection[6,7] do not result in an increased incidence of local recurrence[3,8], and acceptable continence is achieved[9]. In this paper we report the outcome of a vigorous anterior resection policy in 126 consecutive patients with cancer of the lower and midrectum, in terms of morbidity, mortality rate, cancer clearance and continence

Patients and methods

In 126 patients operated on for cancer of the mid or lower rectum, 100 (79 per cent) had anterior resection, 22 (17 per cent) abdominoperineal resection, three (2 per cent) Hartmann's resection and in one the tumour was not resected.

The mean ages of patients for anterior resection and abdominoperineal resection were 65 and 60 years respectively Sixty-two per cent of anterior resections and 72 per cent of abdominoperineal resections were performed in male patients. Tumour height is given in *Table 1* Mean tumour height in abdominoperineal resection was 3 cm and in anterior resection 8 cm Dukes' classification is given in *Table 2*. Surgery was considered palliative in 24 patients (24 per cent) having anterior resections (13 Dukes' 'D'. 11 extensive local spread) and in ten (46 per cent) patients having abdominoperineal resections

Anterior resection methodology

Standard methodology was used. Under anaesthesia, the rectum was irrigated with saline until clear and 50 ml povidone-iodine was instilled A full length midline incision was made. The entire left colon, including the splenic flexure, was mobilized and the left colic artery was ligated The sigmoid colon and complete mesorectum were excised and the descending colon was used for the neorectum

Anastomosis was fashioned with the EEA® (US Surgical Corporation and Auto Suture UK, Ascot, UK) instrument and tested for leakage of air Suction irrigation of the presacral space was performed for 4 days to prevent haematoma. The minimal distal clearance margin was 1 cm. Temporary transverse colostomy was performed in 38 per cent of patients overall but only in 16 per cent of the last 50 patients. A water-soluble contrast enema was performed on 92 patients on the tenth postoperative day.

For the initial 70 cases in the entire series, bladder management was by urethral catheter but for the latter 56 patients fine bore suprapubic catheterization was used Prophylactic subcutaneous low dose heparin was not used during this series, but has now become our practice.

Table 1 *Height of tumour above anal margin in patients* (n = *100*) *who had low anterior resection*

Height (cm)	No of patients
3–5	21
6–7	25
8–9	21
10–12	33

Table 2 *Dukes' classification of the resections*

Dukes' classification	Anterior resection (*n* = 100)	Abdominoperineal resection (*n* = 22)
A	22	—
B	42	9 (41)
C	23	10 (46)
'D'	13	3 (14)

Values in parentheses are percentages

Deaths occurring within 2 months of surgery have been classified as operative mortality Patients were followed up prospectively to monitor recurrence and bowel function The term 'potentially curative resection' was used where removal of the primary tumour was histologically complete longitudinally and laterally with no evidence of distant metastases[10]

Results

Perioperative morbidity accruing from rectal resection is shown in *Table 3*

Three anterior resection patients developed clinical anastomotic leakage. None had a protective proximal stoma In one, the pelvic irrigation system malfunctioned allowing a haematoma to develop. Seven patients developed subclinical radiological anastomotic leakage. In the last 50 patients, clinical leakage was 2 per cent and radiological leakage 6 per cent. No patient died directly as a result of anastomotic leakage One patient, however, became debilitated by such leakage and died of pulmonary embolism. No patient developed anastomotic stricture requiring surgical intervention. Pelvic haematoma resulted in small bowel obstruction in one anterior resection patient.

In 57 anterior resection patients, catheterized urethrally, there was proven urinary tract infection in 19 per cent, in the latter part of the series the incidence was 11 per cent in 43

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Table 3 *Morbidity rates following rectal resection*

Complication	Anterior resection ($n = 100$)	Abdominoperineal resection ($n = 22$)
Clinical leakage	3	—
Small bowel obstruction	1	—
Deep venous thrombosis	7*	2
Pulmonary embolism	5†	1
Pelvic haematoma	1	1
Wound sepsis	6	2
Wound dehiscence	1	—

* Six male patients; † two fatal cases

Table 4 *Neorectal function at 1 year after anterior resection in 80 patients*

Classification	No. of patients	Mean age (years)
Grade 1: perfect	65 (81)	65
Grade 2: incontinent of gas	4 (5)	63
Grade 3: occasional minor leak	7 (9)	59
Grade 4: frequent major soiling	1 (1)	81
Grade 5: colostomy	3 (4)	62

Values in parentheses are percentages

patients catheterized suprapubically. In the entire series two of 126 patients required transurethral prostatectomy for retention.

Bowel function was assessed by interviewing 80 surviving patients 1 year after operation about their bowel function, both at the time of interview and before surgery[11]. Results are shown in *Table 4*. Eighty-one per cent of patients had normal continence. All four patients who had major continence problems (grades 4 and 5) were women and had tumours below 7 cm.

Fifty-five patients underwent anterior resection which the surgeon considered potentially curative, and had a mean follow-up of 42 months (range 24–84 months). Four died of unrelated causes and seven from distant metastases with no evidence of pelvic recurrence. One patient who had a Dukes' C tumour died of local pelvic wall recurrence. A further patient was found 2 years after operation to have a metachronous rectal tumour separate from the suture line, which was treated by a potentially curative Hartmann's resection The incidence of local recurrence in patients with potentially curative tumours was 2 per cent. One of the 12 patients who had a potentially curative abdominoperineal resection developed local recurrence. Of 11 patients having anterior resection who were considered to have extensive local spread at surgery, seven developed pelvic recurrence, two systemic recurrence and two died of unrelated disease within 2 years.

Discussion

Twenty-two per cent of patients who had anterior resection were Dukes' A, while in the abdominoperineal group no patient had Dukes' A disease. Dukes' B and 'D' were roughly of equal incidence for both procedures but there was a 2:1 preponderance of Dukes' C disease in the abdominoperineal group. The disease treated by anterior resection was less severe than that requiring abdominoperineal resection. The earlier the disease is diagnosed the more likely is the patient to retain his sphincters because early tumours, even very low in the rectum, are safely managed by anterior resection. Advanced tumours very low in the rectum require abdominoperineal resection which, alas, is palliative only in about half of our cases.

Much of the morbidity of anterior resection has historically been due to anastomotic dehiscence[1,4] with rates of from 3 to 18 per cent[5,12]. Diminished performance of temporary colostomy[13] (16 per cent colostomy in the last 50 cases) has not resulted in an increased morbidity rate.

For safe colorectal anastomosis, removal of pelvic haematoma is mandatory[14]. Furthermore, the use of sigmoid colon for anastomosis is highly undesirable because it is often narrow, has muscle hypertrophy, may have diverticular disease, and its use, without full left colon mobilization, may result in the presence of intolerable tension at the anastomosis. We undertake full left colonic and splenic flexure mobilization in every case. This, in addition, mobilizes the attachment of the left part of the greater omentum and facilitates its placement in the pelvis. In the early part of the series we unwisely anastomosed cases of extensive pelvic disease. We no longer do this because of subsequent morbidity requiring diversion. Many quoted cases of 'local recurrence' are, in fact, examples of residual tumour, the result of extensive extrarectal ramification, and this is widely recognized as a bad prognostic indicator[15]. True local recurrence is found at or very near the anastomosis, and in its initial stages is superficial and mobile. True local recurrence was seen once in the present series of anterior resections (2 per cent) and even this patient had Dukes' C disease and the recurrence was initially in the side wall of the pelvis. It is considered to be a local recurrence because the operating surgeon decided at the time of resection that the tumour was curable.

This level of recurrence (2 per cent) has been sustained in spite of resections performed extremely close to the tumour and we have shown elsewhere that even with a margin of resection of 1 cm on the gross specimen, involvement of the excised doughnut by tumour is extremely rare[7].

Unquestionably, imperfections of continence sometimes occur and persist following low anterior resection. In this series, 4 per cent of patients had incontinence requiring colostomy, and all were women. It is likely that they were suffering from traction neuropathy of their pelvic nerves[16] and preoperative manometric evaluation has enabled us to predict some patients who may be predisposed to such incontinence[17]. The presence of a poor sphincter pressure profile in a patient who otherwise might have an anterior resection is not an indication for abdominoperineal excision, as a Hartmann's procedure would suffice and spare the patient the morbidity of a perineal wound.

None of our patients had a colonic pouch[18]. After a period of adaptation of up to 12 months after operation, rectal compliance improves in the majority of patients at which time satisfactory continence is achieved[19]. In the present series 81 per cent of patients considered they had normal continence and the majority of the remainder considered their condition acceptable.

Seven per cent of patients with anterior resection developed radiologically confirmed deep vein thrombosis. Five patients developed pulmonary embolism and two died. We had been reluctant to institute a policy of prophylactic subcutaneous low dose heparin in patients requiring such extensive pelvic dissection but all patients are now given prophylactic heparin. Of the patients who developed deep vein thrombosis, all but one were male, and the more difficult problems of the male pelvis may account for this[20].

We conclude that many of the technical difficulties of low anterior resection have been overcome and that acceptable morbidity and mortality rates can be achieved[21]. Improved understanding of the surgical pathology of rectal cancer makes narrow margins of distant clearance acceptable and safe, and the anticipated high level of local recurrence has not emerged. The incidence of serious continence problems following anterior resection is low.

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Non-condylomatous perianal disease in homosexual men

This retrospective study details the findings and outcome in 34 homosexual men, out of a total of 177 patients, who underwent surgery for non-condylomatous perianal disease over a 2-year period. Of 34 homosexuals 20 presented with anorectal sepsis compared with 11 of 79 heterosexual male patients ($\chi^2 = 24{\cdot}07$, $P < 0{\cdot}001$). Lesions included chronic intersphincteric abscess (eight patients), anal fistula (seven patients) and chronic intersphincteric abscess and fistula (five patients). Anal fissure occurred in 15 patients, anal ulcer in three, skin tags in six, haemorrhoids in two and Kaposi's sarcoma in one. Eight patients were human immunodeficiency virus (HIV) antibody negative, four were asymptomatic HIV antibody positive, 12 had symptomatic HIV infection using the Centers for Disease Control classification and in ten patients HIV status was unknown. Irrespective of the type of surgery performed, healing occurred within 6 weeks of operation in all HIV antibody negative patients, all asymptomatic HIV antibody positive and in only one of nine patients with symptomatic HIV infection. Eight of nine patients with symptomatic HIV infection failed to heal by this time ($\chi^2 = 8{\cdot}98$, $P < 0{\cdot}05$). These findings suggest that the prevalence of anorectal sepsis in homosexual men is high and that symptomatic HIV infection is an important determinant of progress after surgery.

Keywords: Homosexual men, perianal disease, HIV infection

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In recent years there has been an increase in the prevalence of gastrointestinal tract diseases in homosexual men[1,2]. The incidence of human immunodeficiency virus (HIV) infection is also rising[3] and it has been estimated that up to 30 per cent of homosexual men with the acquired immunodeficiency syndrome (AIDS) will develop colorectal or perianal diseases and that more than half of these will require surgery[4]. It seems likely, therefore, that colorectal surgeons will become more frequently involved in the diagnosis and management of anorectal problems in homosexual patients.

The relationship between homosexual activity and gut infections due to a wide variety of sexually transmitted, enteric and opportunistic organisms is becoming widely recognized[1,2,5]. Proctitis and proctocolitis are the most usual clinical manifestations, though perianal ulceration can occur. Similarly, condylomata acuminata are prevalent in homosexual men and the association between human papillomavirus infection and these lesions is established[6].

By contrast, other forms of anorectal disease in homosexual men, such as abscess, fistula and fissure, have received less attention and there is a paucity of information concerning the natural history of these types of perianal disease The purpose of the present study was to review the types of lesion and response to surgical treatment in a group of homosexual men with non-condylomatous perianal disease who were referred to a colorectal surgeon (W.W S.) for further management

Patients and methods

The case records of all homosexual patients who underwent surgery for non-condylomatous perianal disease on the colorectal surgery unit at the Middlesex Hospital during the period from November 1986 to December 1988 were reviewed These patients had originally been referred by general practitioners or genitourinary physicians to the outpatient rectal clinic or were inpatient referals from the AIDS ward at the Middlesex Hospital Particular attention was directed towards the duration of symptoms before operation, sexual practices, previous perianal disease, the presence or absence of sexually transmitted disease, HIV antibody status, the type of perianal lesion and the outcome of surgical treatment.

During the same time period, 143 heterosexual patients also underwent operations for perianal disease. There were 79 male patients (median age 45·5 years, range 15–83 years) and 64 women (median age 47 5 years, range 24–80 years) In these patients, the indications for surgery included haemorrhoids in 55 cases, anal fissure in 30, anal skin tags in 28, perianal abscess or fistula in 19, anterior mucosal prolapse in five, squamous carcinoma in three, hydradenitis suppurativa in two and anal stenosis in one patient. The sexual proclivity of the male heterosexual patients had been established by direct questioning during clerking by the house surgeons

For the purposes of the present study HIV status was classified as. HIV antibody negative; HIV antibody positive–asymptomatic, which included patients who were HIV antibody positive but with no stigmata of AIDS as defined by the Centers for Disease Control (CDC)[7]; HIV antibody positive–symptomatic (with past or present stigmata of AIDS and equivalent to CDC groups III and IV), and HIV antibody status unknown

Results

Thirty-four male homosexual patients out of a total of 177 patients who underwent surgery for non-condylomatous perianal disease during the 2-year period were included in the study. The median age of the homosexual patients at presentation with perianal disease was 33·0 years (range 22–54 years) with a median duration of symptoms before surgery of 2·0 months (range 0·25–84 months). All patients gave a history of participation in penoreceptive anal intercourse. Eleven of the 34 patients had previously suffered from condylomata acuminata and ten patients had previous non-condylomatous lesions which had been treated elsewhere.

Associated sexually transmitted disease

Seventeen patients (50 per cent) had evidence of previous sexually transmitted infection which was not present at the time of presentation with their perianal disease. The types of previous sexually transmitted disease included infection with syphilis (11 cases), hepatitis B virus (11 cases), herpes simplex virus (seven cases), gonorrhoea (six cases), cytomegalovirus (two cases) and *Entamoeba histolytica* (one case). At the time of presentation with perianal lesions, three of the 34 patients exhibited active sexually transmitted disease which included cytomegalovirus

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Table 1 *Surgical procedures in 34 homosexual patients*

Procedure	Number
Laying open of abscess or fistula	19
Excision of fissure and sphincterotomy	6*
Anal dilatation and excision of tags	6
Anal dilatation as part of another procedure	2
Haemorrhoidectomy	2
Anal dilatation only	1
Examination under anaesthesia and biopsy	1
Examination under anaesthesia	1

* Includes one patient with anal ulcer

infection in one patient and Herpes simplex infection in two.

HIV status

Eight of the 34 patients were HIV antibody negative and four were HIV antibody positive–asymptomatic (CDC Group II). Twelve patients had symptomatic HIV infection corresponding to CDC Group III in two cases, CDC Group IVa in two, CDC Group IVb in one, CDC Group IVc1 in three, CDC Group IVc2 in three and CDC Group IVd in one patient. Ten patients were not tested for HIV.

Prevalence and types of perianal disease

Forty-seven lesions were encountered in the 34 patients. Anorectal sepsis was present in 20 patients, anal fissure in 15, anal ulcer in three, skin tags in six, haemorrhoids in two and Kaposi's sarcoma in one patient.

Anorectal sepsis. Thirteen of the 20 patients with sepsis had chronic intersphincteric abscesses and in five of these an associated intersphincteric fistula was present. The other seven patients with sepsis presented with anal fistula only. Of these, five were superficial, one was intersphincteric and one was trans-sphincteric. In five of the 20 patients with anorectal sepsis other lesions were present which included anal fissure in three cases and anal ulcer in two. The prevalence of perianal sepsis in the homosexual patients (20 of 34) was significantly greater ($\chi^2 = 24{\cdot}07$, $P < 0{\cdot}001$) than that observed in the heterosexual male patients of whom 11 of 79 underwent surgery for perianal sepsis.

Anal fissures. Only nine of 15 anal fissures were sited solely posteriorly in the anal canal. In the other six patients, the fissure was situated anteriorly in five and both anteriorly and posteriorly in one. Swabs for herpes simplex virus were taken from all fissures and the virus was cultured from two of the 15 patients Six fissures were associated with skin tags, three with anorectal sepsis and two with haemorrhoids The incidence of anal fissures in homosexual men (15 of 34) was not statistically significantly different from that observed in heterosexual male patients (21 of 79; $\chi^2 = 3{\cdot}367$, $P > 0{\cdot}05$).

Anal ulcers. These were situated posteriorly in the anal canal, were oval or circular in shape and between 1 and 2 cm in diameter. They were indolent, with undermined edges, and the base was formed by the internal anal sphincter. One of the three anal ulcers occurred as an isolated lesion, but the other two ulcers were associated with chronic intersphincteric abscesses Two patients had serological evidence of previous cytomegalovirus infection and the cytopathic effects of cytomegalovirus were apparent in biopsy material from one of the ulcers.

Surgical treatment

Nineteen of 20 abscesses or fistulae were laid open. Fissures were treated by either excision and sphincterotomy or anal dilatation (*Table 1*). Examination under anaesthesia and biopsy was the only procedure performed in one patient with chronic intersphincteric abscess because the nature of the lesion was uncertain. The patient with Kaposi's sarcoma underwent examination under anaesthesia only.

Follow-up

Three patients (two HIV antibody positive–symptomatic and one HIV status unknown) defaulted from any follow-up Two other patients were excluded from further analysis. One of these had Kaposi's sarcoma and no operative procedure was undertaken while the remaining patient whose HIV status was unknown underwent biopsy of an intersphincteric abscess which was not considered definitive therapy. Follow-up data for a minimum of 6 weeks after surgery were available for the remaining patients (eight HIV antibody negative, four HIV antibody positive–asymptomatic, nine HIV antibody positive–symptomatic and eight HIV unknown)

Outcome with special reference to HIV status

The proportion of patients with anorectal sepsis and anal fissures was similar in each of the four HIV status subgroups (*Figure 1*). Two of three anal ulcers occurred in HIV antibody positive–symptomatic patients. In the other patient with anal ulcer HIV status was unknown.

Healing of perianal wounds occurred with 6 weeks of surgery in all HIV antibody negative and all HIV antibody positive–asymptomatic patients, but in only one of nine HIV antibody positive–symptomatic patients. Eight out of the nine HIV antibody positive–symptomatic patients had failed to heal by this time and continued to experience symptoms from their perianal lesion This difference in the proportion of patients in each HIV subgroup who exhibited wound healing at 6 weeks was statistically significant ($\chi^2 = 8{\cdot}98$, $P < 0{\cdot}05$). In the eight patients whose HIV status was unknown, six exhibited wound healing at 6 weeks after surgery and two had not healed by this time.

Of those with delayed healing, four of the HIV antibody positive–symptomatic patients failed to exhibit healing at 2, 2,

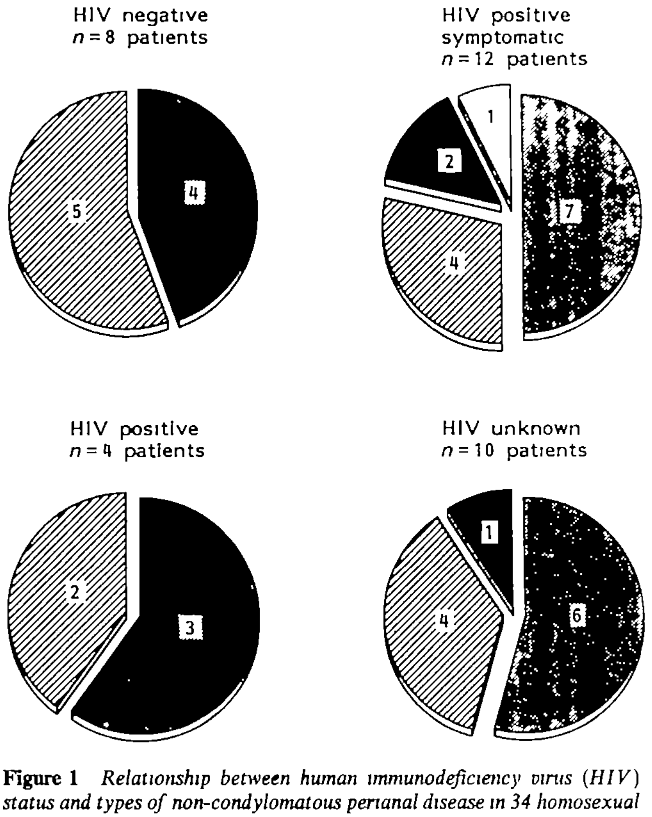

Figure 1 *Relationship between human immunodeficiency virus (HIV) status and types of non-condylomatous perianal disease in 34 homosexual men (values within the pie-chart refer to the number of lesions and not the number of patients which is shown beneath the HIV status),* ▩, *sepsis,* ▨, *fissure,* ■, *ulcer,* □, *Kaposi's sarcoma*

2·5 and 3 months after surgery and were then lost to follow-up. In another four patients with symptomatic HIV infection, healing occurred at 4, 9, 10 and 14 months respectively. Three of these were evaluated by further examination under anaesthesia, but no additional definitive procedure was undertaken. In the two patients with unknown HIV status and delayed healing, one healed successfully at 11 months and the other has not healed 10 months after operation.

Discussion

It is well known that perianal disease in homosexual men may be caused by specific infections[1,2]. Herpes simplex virus can produce multiple perianal ulcers, and painful chancres may accompany primary syphilitic infection[8]. The anorectal region is also a primary target for the opportunistic infections of AIDS, and several authors have noted that organisms not traditionally associated with sexual transmission, such as cytomegalovirus and *Cryptococcus neoformans*, may, in the presence of HIV infection, cause painful anal ulceration[5,9,10,11]. Clearly, all male homosexual patients, particularly those with symptomatic HIV infection, who present with perianal disease should be carefully screened for the presence of an infective agent. Nevertheless, the findings from the present study, in which fewer than 10 per cent of patients had active sexually transmitted disease, illustrate that perianal disease in homosexual men is not always due to sexually transmitted or opportunistic infection.

The spectrum of non-condylomatous perianal disease in the homosexual population has been previously examined by Sim[12]. He reviewed 251 anorectal procedures carried out on 'no-risk' heterosexual and 'at-risk' homosexual patients and demonstrated that both groups displayed similar types of perianal disease. Excluding patients with condylomata acuminata, 65 of 187 'no-risk' and 17 of 45 'at-risk' patients presented with either anal sepsis or fistula[12]. By contrast, in the present series almost two-thirds of homosexual men presented with anorectal sepsis and this proportion was statistically highly significantly greater than that observed in heterosexual male patients who underwent operation over the same period of time. Wexner *et al.*[4], in their study of anorectal disease in male homosexual patients with symptomatic HIV infection, noted that abscess or fistula was the main indication for surgery in 30 of 51 patients. These findings are similar to those of the present study and lend support to the view that the prevalence of anorectal sepsis in homosexual men is high.

The severe and progressive forms of anorectal sepsis that have been reported in patients with AIDS[4,12] were not encountered in the present series. Nevertheless, our findings are in keeping with those of Sim[12] and others[13] who have also noted that chronic abscesses and intersphincteric sepsis are particularly common in homosexual men. The reasons for this are uncertain but, as suggested by Baker and Peppercorn[2], repeated trauma due to receptive anal intercourse and other homosexual practices is likely to be an important aetiological factor. A similar mechanism may also explain the occurrence of atypically situated anal fissures and chronic anal ulcers in these patients.

It has been stated that healing usually proceeds uneventfully in the presence of AIDS[12]. In contrast to this, Wexner *et al.*[4] found that 88 per cent of perianal wounds had not healed 30 days after operation. Our data support those of Wexner *et al.* and indicate that a high proportion of patients with symptomatic HIV infection exhibit delayed healing of perianal wounds and experience considerable morbidity for weeks or months after surgery. These observations are of great concern and carry important therapeutic implications in that, unless the subgroup of homosexual men with symptomatic HIV infection is identified preoperatively by careful clinical examination, serological testing or the assessment of risk factors[14], they may be subjected to operative procedures which exacerbate rather than improve their perianal disease. In the current climate, where HIV testing can only be performed after full consent, it may be that all male homosexual patients should be regarded as potentially symptomatic HIV positive and managed as conservatively as possible.

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Podophyllin versus scissor excision in the treatment of perianal condylomata acuminata: a prospective study

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Thirty-seven patients with previously untreated perianal condylomata acuminata were randomly treated by application of 25 per cent podophyllin or scissor excision. The result of treatment was assessed by an independent observer. At 6 weeks, scissor excision completely cleared the warts from 16 of 18 patients (89 per cent) compared with 15 of 19 patients (79 per cent) treated with podophyllin. Following complete clearance by surgery, two patients had recurrent warts at 18 weeks and a further single patient at 42 weeks, giving a cumulative recurrence rate of 19 per cent. In contrast, five of 15 patients whose warts were cleared by podophyllin had recurrent warts at 18 weeks and a further four at 42 weeks representing a cumulative recurrence rate of 60 per cent ($\chi^2=3{\cdot}95$, *d.f.* $=1$, $P=0{\cdot}05$)*. At 42 weeks six patients (32 per cent) were free of disease in the podophyllin group compared with 13 (72 per cent) in the scissor excision group* ($\chi^2=4{\cdot}6$, *d.f.* $=1$, $P=0{\cdot}03$)*. Scissor excision is therefore preferable to podophyllin application in the treatment of perianal condylomata acuminata.*

Keywords: Condylomata acuminata, podophyllin, scissor excision

Condylomata acuminata (venereal warts) are due to infection with human papillomavirus[1] and present a major public health problem which is increasing in prevalence[2,3]. Treatment of these lesions is generally acknowledged to be difficult, time consuming and to give poor results. The aim of this prospective randomized, controlled study was to compare podophyllin application and scissor excision in the treatment of perianal condylomata acuminata.

Patients and methods

Thirty-seven patients with previously untreated condylomata acuminata entered the trial Patients with genital and/or anal canal involvement above the dentate line, those suffering from other perianal diseases and those receiving topical perianal medication were not included in the study Other exclusion criteria included pregnancy and patients receiving antiviral, immunosuppressive therapy or immune stimulation therapy within 2 months. All sexual partners were examined and treated if necessary. Patients were strongly advised to refrain from sexual intercourse during the treatment period and told to use a condom for 4 months after completion of treatment

The patients were randomly assigned according to the last digit of the number of their hospital notes to treatment with scissor excision or local application of 25 per cent podophyllin in benzoin tincture. The investigator was not aware of the patients' hospital number at time of randomization Scissor excision was carried out according to the method described by Thomson and Grace[4] If the lesions were numerous they were removed in two stages at a 3-week interval. Podophyllin application was as described by Simmons[5] and the treatment was repeated weekly for up to 5 weeks if necessary

Follow-up was carried out by an independent observer, who had no knowledge of the treatment given, at 6, 18 and 42 weeks after the start of treatment. The presence of condylomata acuminata at 6 weeks' follow-up was considered as failure of treatment. The Mann–Whitney U test and χ^2 test with Yates' correction were used for comparison between groups. Confidence intervals were calculated according to Gardiner and Altman[6].

Results

In all, 19 patients were treated with podophyllin and 18 with scissor excision. The two groups were comparable (*Table 1*).

Table 1 *Comparability of groups*

	Podophyllin group ($n=19$)	Surgical group ($n=18$)
Median (range)		
Age (years)	33 (20–51)	30 (21–49)
No. of lesions	14 (6–34)	15 (5–36)
Duration of symptoms (weeks)	12 (7–26)	11 (8–24)
Male:female	12:7	13:5
Number of homosexuals	7	6
Number of females practising anal intercourse	2	1
Number of patients with anal canal lesions below dentate line	3	5

All patients completed the 42 weeks of follow-up. At 6 weeks, scissor excision had completely cleared the warts from 16 of 18 patients compared with 15 of 19 patients treated with podophyllin, giving a failure rate of 11 and 21 per cent respectively. After complete clearance by surgery, two patients had recurrent warts at 18 weeks and a further single patient at 42 weeks, giving a cumulative recurrence rate of 19 per cent In contrast, five of 15 patients whose warts were cleared by podophyllin had recurrent warts at 18 weeks and a further four at 42 weeks, representing a cumulative recurrence rate of 60 per cent. The cumulative recurrence in the podophyllin group was significantly higher than in the scissor excision group ($\chi^2=3{\cdot}95$, d.f. $=1$, $P=0{\cdot}105$; difference 41 per cent, 95 per cent confidence interval 10–73 per cent). At the end of follow-up, six patients (32 per cent) were disease free in the podophyllin group compared with 13 (72 per cent) in the scissor excision group ($\chi^2=4{\cdot}6$, d.f. $=1$, $P=0{\cdot}03$; difference 40 per cent, 95 per cent confidence interval 11–70 per cent) Podophyllin treatment required multiple weekly applications (median 4, range 3–5), whereas surgical treatment was completed in one session in 16 patients and two sessions in two patients. There were no

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documented postoperative complications and none of the patients had anal canal scarring and/or stenosis or required the use of an anal dilator.

In the surgical group, 11 patients experienced pain and/or discomfort which required analgesia, compared with five patients in the podophyllin-treated group. One patient had skin burns in the podophyllin group. None of the side-effects were severe enough to warrant cessation of treatment, and pain responded to oral analgesia (paracetamol) in all cases. Sixteen (89 per cent) of the patients treated by surgery were satisfied with their treatment whereas only nine (47 per cent) of the patients treated with podophyllin were satisfied.

Discussion

Condylomata acuminata represent an important sexually transmitted disease[2,3]. Untreated lesions are most likely to persist for a long time, and give rise to distressing symptoms of perianal discomfort, irritation and occasional bleeding Rarely patients may have spontaneous regression[7] There is evidence that malignant changes can occur in these lesions[8,9] and that human papillomavirus is associated with genital and anal carcinomas[1]. There is therefore a need for effective therapy.

The factors affecting the outcome of this disease are poorly understood. The role of host immunity is suggested by the extensive refractory disease associated with immunosuppression and the 20 per cent rate of spontaneous remission in healthy subjects during the first year of infection[7]. Conventional therapy involves destruction of warty tissue with topical drugs or surgery. Recurrences are frequent, probably due to subclinical infection, and it is not clear if a virological cure is ever achieved in any patient. Existing studies are not comparable in patient selection, methods used to monitor response, and follow-up. Local application of podophyllin[5], 5-fluorouracil[10], thiotepa[11] and colchicine[12] produces variable results. Topical drugs usually give incomplete clearance in some patients at initial therapy and high recurrence rates. Surgical treatment with cryosurgery[13], electrocautery[14] and laser[15] may be more effective but these methods are painful and may produce scarring. Laser therapy is costly and not readily available. Scissor excision of the lesions offers the advantage of preserving the small but healthy skin bridges between the warts, thus promoting healing without scarring.

Thomson and Grace[4] reported a 1-year recurrence rate of 39 per cent in a non-randomized study of 75 patients with perianal and anal warts treated by scissor excision. The lower recurrence rates in this study and in others[16,17] may be because of differences in the study population.

In this study, the only side-effects detected were perianal skin burns and pain, which responded to paracetamol in all cases. The higher incidence of pain in the surgical group is to be expected and is in agreement with the findings of Jensen[16]. The low incidence of chemical skin burns in the podophyllin-treated group may be due to the careful application of the drug, avoiding the adjacent skin, and the graded time for which the preparation was left on the lesions[5].

This study demonstrates that scissor excision is a safe method of treatment of perianal condylomata acuminata and produces faster clearance and lower recurrence rates than local application of 25 per cent podophyllin. Our current approach to therapy seems irrational as condyloma acuminatum represents a viral infection of both abnormal and normal appearing epithelium. Antiviral drugs and immune modulators might be a more effective therapy. Interferons show promise[18,19], but their efficacy has been modest and no greater than that of surgery[17]. An effective treatment for condylomata acuminata remains elusive, but a combination of local removal (e.g. surgical excision) and adjuvant therapy (e.g. interferon) may be the answer.

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Lipids in breast carcinogenesis

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Excess dietary fat has been identified as a risk factor in the development of human breast carcinoma. However, the quality of fat may be more important than the overall quantity. We have studied the growth of human MCF7 breast carcinoma xenografts in athymic mice treated with dietary supplements of N-6 and N-3 series essential fatty acids given as natural preparations of evening primrose oil and fish oil. Olive oil and normal laboratory diet lacking the essential fatty acids served as controls. Animals treated with essential fatty acids developed tumours which were significantly smaller than both control groups (Mann–Whitney U test, $P<0{\cdot}001$). Median tumour weights according to diet were: evening primrose oil, 133 mg; fish oil, 70 mg; olive oil, 212 mg, and control, 270 mg. Nutritional intervention to increase the proportion of essential fatty acids in the diet may have a role in the management of breast carcinoma.

Keywords: Breast carcinoma, diet, prevention, essential fatty acids

The aetiology of human breast cancer is poorly understood. It is known that an interplay between heredity and environmental factors initiate and/or promote the disease. Factors associated with high risk have been identified as family history, menstrual history, sex hormone levels, viral infection and previous benign disease. Diet is also implicated in the pathogenesis of breast cancer. This is based on the existence of a widely varying incidence of breast cancer throughout the world which strongly correlates with the amount of fat eaten[1]. Breast cancer is common in western Europe and North America where some 140 g of fat are consumed daily (40 per cent of total calories or 20 per cent by weight) which is some five times higher than the traditional Japanese diet based on rice and seafood. Corresponding to this difference in fat intake, the European countries have an incidence of breast cancer three or four times higher than that found in Japan and Asia.

Circumstantial evidence provided by epidemiological studies is further supported by laboratory animal models of fat and breast cancer. These have repeatedly shown over the past 40 years that high levels of dietary fat, in the order of 20 per cent by weight or 40 per cent by calories which mimic the human diet, promote mammary tumour growth in rats and mice[2–4]. This finding holds true regardless of how the tumour is initiated, whether spontaneous[2,4], chemically induced by nitrosomethylurea or dimethylbenzanthracene[5], solid tumour allografts[6] or by irradiation[6,7]. The crucial threshold for tumour promotion seems to be about 10–20 per cent by weight. Numerous fats and oils have been studied and found to promote tumour growth.

However, recent interest has turned to a singular subgroup of lipids, the essential fatty acids, and it appears that they may have antitumour properties. Essential fatty acids are characterized by the presence of several double bonds in the carbon skeleton and are essential dietary requirements, rather like vitamins, because they cannot be synthesized *de novo* in the human body. The N-6 series commencing with linoleic acid are derived from plant sources and the N-3 series from fish oils. They are important structural components of all cell membranes and give rise to a variety of intermediates such as prostaglandins and leukotrienes and are thought to have wide-ranging influences on the immune system, autocrine–paracrine growth regulation and the mediation of inflammation. Linoleic acid is present in many of the polyunsaturated vegetable oils but γ-linolenic acid is relatively scarce, being found in abundance in relatively few forms such as evening primrose oil, blackcurrant seed oil and borage. Deficiency of the essential fatty acids in rodents is characterized by weight loss, dermatitis, sterility, increased susceptibility to infection and premature death[8]. Human beings on long-term parenteral nutrition lacking these essential fatty acids will also develop dermatitis which can be corrected by the supplementation of γ-linolenic acid[9].

Of greater interest is the recent finding that the essential fatty acids might have antitumour properties. A South African group has been foremost in testing essential fatty acids against numerous human cancers *in vitro*. They have shown that γ-linolenic acid can inhibit squamous oesophageal carcinoma, hepatoma, osteogenic sarcoma and laryngeal carcinoma cells without harming normal bovine kidney cells[10–13]. A Canadian group added to the growing list of cancer cell types in showing that human breast adenocarcinoma ZR751, lung A549 and prostatic carcinoma PC3 could be killed or inhibited by the essential fatty acids linoleic, γ-linolenic, arachidonic, eicosapentaenoic and docosahexaenoic acids at concentration of 20 μg/ml[14].

The purpose of this study was to investigate the role of essential fatty acid dietary supplements in the growth of a human breast carcinoma cell line *in vivo* in an animal model. Diets rich in N-6 or N-3 essential fatty acids were compared with controls lacking those essential fatty acids

Materials and methods

Animals

MF1 nu/nu/ola athymic mice were obtained from Harlan Olac, Bicester, UK and subsequently bred in our animal unit Mice were housed in groups of three in polycarbonate cages fitted with filter lids. The mice were maintained in a dedicated, clean isolation unit. Room temperature was controlled at 24°C and 12-h light and dark periods alternated.

Cell cultures

The MCF7 cell line was used as an example of human breast carcinoma It is an oestrogen-dependent cell line derived from the malignant pleural effusion of a postmenopausal woman with breast carcinoma[15]. Normal breast fibroblasts were derived from samples of breast tissue obtained from women undergoing surgery for benign breast disease. Tissue was enzymatically disassociated and separated into cell types by gravity sedimentation as described elsewhere[16]. Cells were maintained in monolayer tissue culture in RPMI 1640 medium (Gibco Ltd., Paisley, UK) supplemented with 10 per cent fetal calf serum (Gibco Ltd), human monocomponent insulin 120 units/l (Novo Industries, Romford, UK) hydrocortisone 10 mg/l (Sigma Chemical Company Ltd , Poole, UK), benzylpenicillin 60 mg/l (Glaxo Laboratories Ltd., Greenford, UK), streptomycin 100 mg/l (Evans Medical Ltd., Dunstable, UK) and amphotericin 2 mg/l (E. R Squibb Ltd., Hounslow, UK) Cultures were maintained at 37°C in an atmosphere of humidified air enriched with 5 per cent carbon dioxide.

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Tumour cell inoculations

The method of Horgan *et al.*[16] was used: MCF7 and fibroblast cells were trypsinized from culture flasks. Cell viability was >95 per cent as assessed by trypan blue exclusion. Cells were counted in a haemocytometer. Two million MCF7 cells mixed with two million fibroblasts were suspended in 100 µl culture medium and injected into the right hind quarter mammary fat pad of anaesthetized female athymic mice that were 6–8 weeks old. An oestradiol pellet was inserted subcutaneously on the dorsum of each mouse to meet the hormone dependence of the MCF7 cell line.

Diets

Mice were divided into four dietary groups

Group 1: Control mice (n = *24*). These mice received a stock commercial rodent diet (Pilsbury Ltd., Birmingham, UK) which contains 4 per cent by weight total lipid of which 1·5 per cent is linoleic acid and 0·08 per cent γ-linolenic acid.

Group 2. Olive oil 10 per cent weight for weight supplement (n = *24*). This group provided an additional control as olive oil contains no essential fatty acids but 65 per cent oleic acid and 14 per cent linoleic acid

Group 3 Evening primrose oil 10 per cent weight for weight supplement (n = *24*) Evening primrose oil is one of the richest known sources of γ-linolenic acid, 9 per cent weight for weight and linoleic acid, 70 per cent weight for weight.

Group 4 Fish oil 10 per cent weight for weight supplement (n = *24*). Fish oil contains N-3 series essential fatty acids, eicosapentaenoic acid 28 per cent weight for weight and docosahexaenoic acid 5 per cent weight for weight

The control diet pellets were ground to crumbs and thoroughly mixed with the chosen oil in a domestic foodmixer. Diet was freshly prepared every 5 days and stored in air tight boxes at 4°C. A surfeit of diet was available *ad libitum* to the mice and replenished daily. Olive oil, evening primrose oil and fish oil were donated by Scotia Pharmaceuticals, Guildford, UK

Experimental protocol

Athymic mice were weaned and maintained on normal diet until they were 6–8 weeks old. They were then started on the appropriate diet for 1 week in an effort to stabilize tissue levels with the new fatty acids. MCF7 fibroblast cell inoculations were given in the mammary fat pad. Over the ensuing weeks the liquid blister was absorbed and was replaced by a solid tumour mass Five weeks later the animals were killed with an overdose of ether. Tumours were dissected out from the membranous fat pad and weighed; they were either fixed in formalin for histological examination or snap-frozen in liquid nitrogen for subsequent fatty acid analysis. The frozen tumours, identified only by a code number, were shipped to Scotia Research Institute, Kentville, Nova Scotia; the fatty acids were extracted by the method of Folch *et al*[17] and analysed by gas liquid chromatography as described elsewhere[18].

Data analysis

Tumour weights and mouse body-weights were described non-parametrically by median and interquartile range. The Mann–Whitney *U* test was used for comparison of the data. Results were accepted as statistically significant when $2P<0{\cdot}05$

Results

All 96 mice in the four dietary groups remained healthy during the course of the experiment without overt signs of infection and no premature deaths. Each mouse consumed about 5 g diet daily and all mice gained body-weight. There was no significant difference in the amount of body-weight gained, about 4 g, by the mice in the various dietary groups (*Table 1*). The tumour model worked well with 92 of 96 mice developing a solid tumour. Tumours grew as discrete solid nodules and were readily identified and removed from the filamentous, connective adipose tissue of the mammary fat pad. On histological examination the MCF7 tumours were seen to be highly cellular consisting of epithelioid cells arranged in sheets in a fine, fibrous stroma The inclusion of fibroblasts with the MCF7 cells in the inoculum did not produce fibrous overgrowth. Tumours taken from mice which were fed the various lipid diets were identical both macroscopically and microscopically.

Table 1 *Effect of dietary supplementation with lipids on mouse body-weight*

Diet	*n*	Gain in body-weight (g) Median	 Interquartile range	$2P$*
Control	24	4·3	1 9–5·8	—
Olive oil 10%	24	4·5	3·4–5·4	0 54 n.s.
Primrose oil 10%	24	4·1	3·0–5·4	0·71 n.s
Fish oil 10%	24	5·5	3 4–6 4	0·06 n.s

* Comparison of control and test group by Mann–Whitney *U* test: n.s., not significant

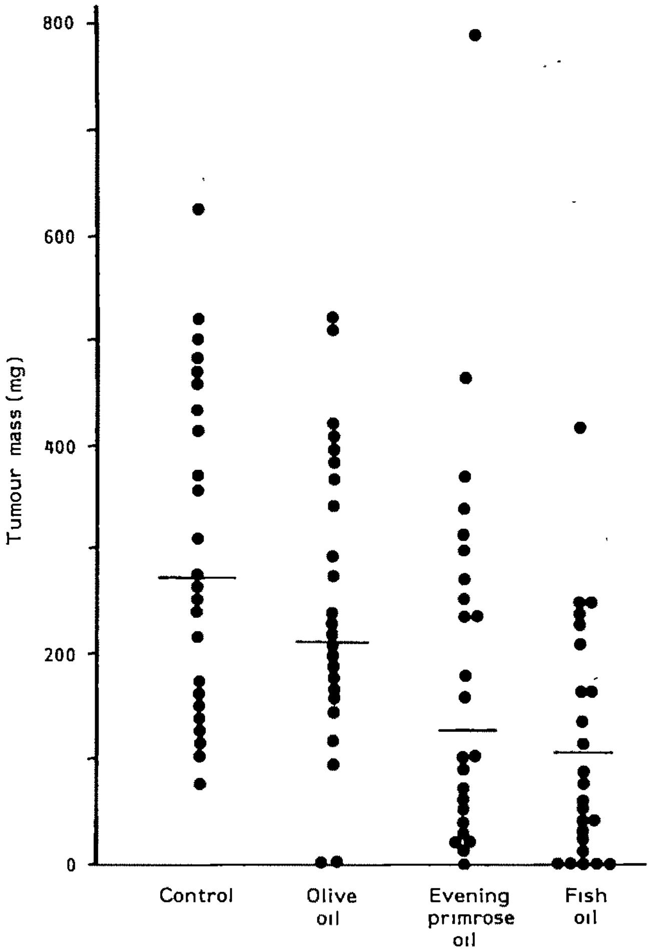

Figure 1 *Scattergrams showing individual MCF7 tumour weights according to diet. Bars indicate median values*

The range of tumour weights was 0–795 mg. Individual tumour weights according to diet are shown as scattergrams in *Figure 1*. A descriptive non-parametric summary of tumour weights is shown in *Table 2*. Those animals fed the usual laboratory diet as controls developed tumours with a median weight 270·5 mg. Feeding a 10 per cent olive oil supplement, with virtually no additional fatty acid, did not influence tumour growth in any way compared with controls ($2P = 0{\cdot}34$) with a median tumour weight of 212 mg. Feeding the mice supplements of N-6 or N-3 series essential fatty acids as primrose oil and fish oil significantly inhibited tumour growth. Mice treated with 10 per cent evening primrose oil developed tumours which were half the size of controls (median tumour weight 133 mg *versus* 270 mg, $2P<0{\cdot}009$). The fish oil

Table 2 *Effect of dietary lipid supplementation on MCF7 tumour weight*

Diet	n	Tumour weight (mg) Median	 Interquartile range	$2P$*
Control	24	270·5	148·7–452·7	—
Olive oil 10%	24	212·5	157·5–375·2	0·34 n.s.
Primrose oil 10%	24	133·0	37·3–296·7	0·009
Fish oil 10%	24	70·0	19·2–205·0	0·001

* Comparison of control and test group by Mann–Whitney *U* test: n.s., not significant

Table 3 *Effect of diet on fatty acid composition of MCF7 tumours*

Fatty acid	Fatty acid nomenclature*	Fatty acid content in MCF7 tumours Control	 Olive oil	 Primrose oil	 Fish oil
Myristic	14:0	1·8	1·0†	1·0†	4·1†
Palmitic	16:0	20	14·4†	15†	21·1
Palmitoleic	16:1	10·6	6·1†	6·6†	10·8
Stearic	18:0	4·4	3·8	4·7	4·7
Oleic	18:1	33·7	49·7†	20·2†	27·2†
Linoleic	18:2	16·4	13·9†	31†	14·0†
γ-Linolenic	18.3	0	0	1·4†	0
Dihomo-γ-linolenic	20.3	0·18	0·15	0·46†	0·14
Arachidonic	20.4	2·7	2·0	4†	1†
Eicosapentaenoic	20:5	0·04	0	0	2·2†
Adrenic	22:4	0·3	0·2	0·4	0·15†
Docosahexaenoic	22:6	1·0	0·8	0·85	1·4†

* Fatty acid nomenclature describes number of carbon atoms:number of double bonds in the molecule. Values are the median percentage, the Mann–Whitney *U* test is used to compare median percentage fatty acid content of control *versus* each test group. † $2P < 0{\cdot}001$

dietary group developed tumours of median weight 70 mg, again significantly smaller than control, $2P < 0{\cdot}001$. There was no difference in the efficacy of tumour inhibition achieved by either primrose oil or fish oil ($2P = 0{\cdot}09$).

Tumour fatty acids

Fifteen tumours from each dietary group were analysed for dietary fatty acid content: the results are shown in *Table 3*. Tumours taken from mice fed the control diet were rich in unsaturated and monounsaturated fatty acids, chiefly palmitic, palmitoleic and oleic acids. Supplementation with all three polyunsaturated lipids, olive oil, primrose oil and fish oil, reduced the proportion of unsaturated fatty acids to polyunsaturated fatty acids. The exact balance of fatty acids reflected the particular diet. Thus, olive oil which comprises 65 per cent oleic acid increased the amount of oleic acid appearing in the tumour tissue. Evening primrose oil diet rich in the N-6 series essential fatty acids produced a significant rise in the tumour levels of linoleic, γ-linolenic, dihomo-γ-linolenic and arachidonic acids. Similarly, fish oil containing the N-3 series essential fatty acids resulted in the accumulation of those particular fatty acids, eicosapentaenoic and docosahexaenoic acids.

Discussion

The evidence of an epidemiological association between dietary fat and the development of breast cancer is strong and is supported by numerous animal models. It has been repeatedly shown that high levels of dietary fat, >10 per cent by weight, promote mammary tumour development whereas very low fat diets, <5 per cent by weight, and particularly fat-free diets inhibit tumour growth[2,5–7,19–22]. Unfortunately, however, it is unrealistic to expect humans to eat a totally fat-free diet, however beneficial. None the less, eminent American authorities have already advocated a drastic reduction in the amount of fat consumed from 40 to 20 per cent of calories[23,24]. With the recent realization that the balance of fatty acids may be more important than the total quantity, the current experiments have attempted to maintain an acceptable level of fat in the diet yet increase the proportion of polyunsaturates and essential fatty acids. Several independent groups have shown that the N-6 series essential fatty acids in evening primrose oil and N-3 essential fatty acids in menhaden marine oil (Zapata Haynie Corporation, Reedville, USA) and *Maxepa* fish oil (Duncan, Flockhart and Company Ltd., Greenford, UK) will significantly inhibit the growth of species-specific mammary tumours induced in rats and mice[25–30].

The advantage of the presently described athymic mouse model is that it allows an *ex vivo–in vivo* assessment of human breast carcinoma to these lipids. Athymic mice have a congenital absence of the thymus gland and hence lack T cell mediated immunity and are unable to reject foreign species' xenografts. This is the first report of a human breast carcinoma cell line being susceptible to treatment with essential fatty acids. Both evening primrose oil and fish oil were equally effective in limiting tumour growth by 51 per cent and 74 per cent respectively of control growth. Olive oil, which is devoid of essential fatty acids, had no effect on tumour growth. Two previous studies[25,26] found that 200 μl evening primrose oil daily given either by stomach tube or parenteral injection restricted rat R3230AC mammary tumour growth by 25–50 per cent. However, this dose level is difficult to extrapolate to possible human use. The advantage of using a specified 10 per cent by weight dose level is that some relevance to human doses may be made. A fat level of 10 per cent by weight provides 20 per cent of total calories and in human terms some 50 to 60 ml of primrose and fish oil would meet this requirement. This seems a somewhat high dose but is none the less practical, and improved pharmacological preparations of highly concentrated fatty acids may make delivery even simpler in future. There are now several pointers that essential fatty acids have antitumour properties but the mechanism of their effect is poorly understood. The present study showed that the N-6 and N-3 series essential fatty acids accumulated in the relevant tumours but it is unknown whether structural changes in cell membranes were responsible for the change in biological properties or whether the fatty acids simply acted as substrates for other intermediates to exert the effect.

There are several hypotheses to explain the possible mode of action of essential fatty acids. The essential fatty acids are obligate precursors of prostaglandins of the 1, 2, 3 and 4 series and it is well recognized that prostaglandins can influence malignant cell behaviour. For example, many cancers produce excessive amounts of the 2 series prostaglandins and yet are unable to manufacture prostaglandin E1[31], which is itself tumoricidal to DMBA-induced mammary tumours *in vitro*[32]. Some studies infer an opposing tumour-promoting action to certain prostaglandins because anti-inflammatory drugs such as flurbiprofen and indomethacin, which inhibit prostaglandin synthesis, are able to restrict tumour growth in mice[33] and even counteract the tumorigenic effect of a high fat diet[34]. Whilst the action of essential fatty acids may be expressed via derived prostaglandin products it is difficult to predict or control which of the many prostaglandin classes would gain by simple provision of additional dietary substrate.

Figure 2 shows a flowchart of the synthesis of N-3, N-6 and N-9 polyunsaturated fatty acids. One enzyme, Δ-6-desaturase, catalyses the same crucial desaturation step in all three pathways[35]. Many, if not all, transformed and malignant cells lose this enzyme[36,37] and consequently the intracellular synthesis of longer chain polyunsaturated fatty acids is arrested. Further support for this enzyme deletion is found in the work of Wood *et al.*[38] who described a fall in the stearic:oleic acid ratio in red cell membranes of patients suffering from a variety of cancers. This was considered to be a non-specific marker for cancer but no explanation was offered about the mechanism. In the light of Δ-6-desaturase enzyme deletion it can be seen from *Figure 2* that whilst stearic acid may be converted to oleic

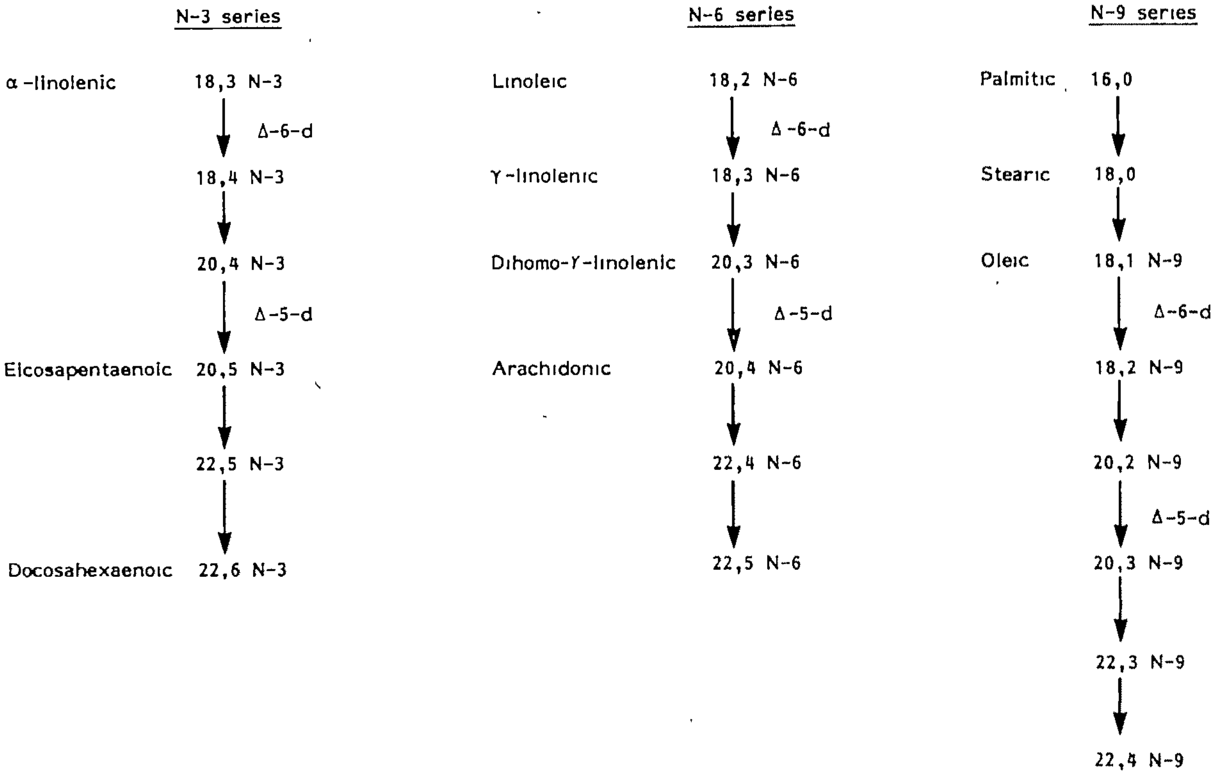

Figure 2 *Biosynthesis of N-3, N-6 and N-9 series polyunsaturated fatty acids. Δ-5-d and Δ-6-d represent the desaturase enzymes creating double bonds at the 5 and 6 carbon positions*

acid the enzyme deletion will prevent further metabolism of oleic acid. Oleic acid will therefore accumulate and the ratio of stearic to oleic acid will fall. The effects of the Δ-6-desaturase enzyme deletion can theoretically be overcome by exogenous supply of γ-linolenic and eicosapentaenoic acids which are capable of entering the pathways at later stages. The restored metabolic function might go some way to restoring normal regulation of cellular activity.

Polyunsaturated fatty acids and essential fatty acids containing several double bonds are unstable molecules and are readily oxidized by non-specific and specific lipoxygenase and cyclo-oxygenase enzyme systems to yield free lipid radicals and peroxides which are toxic to cells. Horrobin's group reported that the human breast adenocarcinoma ZR751 was killed by treatment with essential fatty acids *in vitro* and they found increased levels of lipid peroxides and superoxide anions within the cells as shown by nitro blue tetrazolium reduction and the high content of thiobarbituric acid reactive material[39]. Vitamin E, an antioxidant which scavenges free radicals, blocked this cytotoxic effect. Yet another mechanism is the subtle regulation of cell growth at a local level. Lippman's group have shown that oestrogen and progestin hormones act on breast cancer cells as mitogens by inducing the secretion of a variety of peptides, such as insulin-like growth factor 1, which have a role as autocrine and paracrine growth regulators[40]. Some of these growth regulatory factors are themselves essential fatty acids[41]. Progestins inhibit MCF7 growth *in vitro* by inducing a 72 kilodalton protein which has identical biochemical properties to the enzyme fatty acid synthetase[42].

Thus it can be seen that there is a logical explanation for the involvement of fats in breast carcinogenesis. The National Cancer Institute in the USA is already so convinced of the circumstantial evidence linking high fat diets and breast carcinogenesis that they have initiated studies of dietary intervention in women with advanced breast cancer and also proposed low fat diets as adjuvant therapy for women at risk of developing the disease[24]. On the basis of the present work we would suggest that the proposed reduction of total fat does not go far enough. We would advocate that the balance of fatty acids in the diet must be altered to increase the proportion of essential fatty acids. This might be achieved by simple changes in dietary practice to consume more sea food and reduce the amount of animal fat eaten or take the form of dietary supplements of specific essential fatty acids. Dietary intervention may well prove to be a useful adjunct to existing therapies in the treatment of breast cancer.

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Postsplenectomy sepsis

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This review examines the infectious consequences of elective and emergency splenectomy, highlighting the importance of infection with Streptococcus pneumoniae. *The influence of splenectomy on the immune system is discussed and the efficacy of vaccines in preventing postsplenectomy sepsis is reviewed. The value of alternative methods of preventing postsplenectomy sepsis is considered.*

Keywords: Splenectomy, infection, pneumococcal vaccine

Despite the increasing use of splenic conservation emergency splenectomy is still performed frequently, and elective splenectomy, although now rarely used to stage lymphoma, is still performed for giant splenomegaly, hairy-cell leukaemia and idiopathic thrombocytopenic purpura. As a result, postsplenectomy sepsis remains an important topic.

The clinical appearance of postsplenectomy infection varies from a mild pneumonia to a fatal overwhelming sepsis[1–10] and clinicians have attempted to reduce such infections by immunizing against the common infecting organisms, administering prophylactic antibiotics and, more recently, by employing splenic conservation. However, despite widespread use of prophylactic antibiotics and capsular polysaccharide vaccines, there is extensive discussion over many aspects of their use, and the place of partial splenectomy and/or splenic autotransplantation is unclear.

In order to formulate guidelines for the prevention of infection in the asplenic patient we have reviewed the available literature and attempted to answer the following questions: (1) what are the infectious consequences of splenectomy; (2) how does removal of the spleen alter the immune system, and how effective are vaccines in preventing postsplenectomy infection; (3) are other methods of sepsis prophylaxis worthwhile?

What are the infectious consequences of splenectomy?

Characteristics of postsplenectomy infection

Ellison and Fabri[1] list the complications of splenectomy as respiratory complications, haemorrhage, splenic abscess, injury to adjacent structures, thrombosis and thrombocytosis, postsplenectomy infection and unexplained fever. In addition they suggest that 'postsplenectomy infection represents a spectrum of infectious processes. In its mildest form lobar pneumonia may occur while its more severe form is that of overwhelming and fatal infection, the onset of which is often subtle yet sudden, and the focus often obscure.' Alternatively, postsplenectomy sepsis has been defined by Singer[2] as 'septicaemia, meningitis or pneumonia, usually fulminant, but not always fatal, occurring days to years after removal of the spleen.'

Interest in the phenomenon of postsplenectomy sepsis was aroused by the observations of King and Shumacker[3] in 1953. They described five cases of fulminant sepsis in infants who had undergone splenectomy for congenital spherocytosis. Since then various degrees of severity have been described but commonly postsplenectomy sepsis presents as an overwhelming infection with multiorgan failure[4]. Diamond[5] in 1969 first coined the term 'overwhelming postsplenectomy infection' (OPSI) to describe a fulminant bacteraemia which can lead to a rapid demise. The following characteristics of OPSI were described by Van Wyck[6] in 1983: extraordinarily fulminant course, frequent absence of a septic focus, bacteraemia, coma, shock, consumptive coagulopathy and adrenal haemorrhage (Waterhouse–Friderichsen syndrome). An interesting feature is the high number of bacteria found in the blood of these patients. More than one million bacteria per millilitre are often found in the blood of splenectomized septic individuals, while non-splenectomized septic individuals[7] rarely show more than one thousand organisms per millilitre.

Incidence and mortality of postsplenectomy infection

Estimates of the frequency of occurrence and the mortality associated with postsplenectomy sepsis vary. The reason for this variability can, to some degree, be understood when the differences between the various studies are appreciated Firstly, postsplenectomy sepsis is a rare event, so large patient populations with large control groups are needed to estimate the incidence reliably. Secondly, the definitions of postsplenectomy sepsis and OPSI vary from study to study. Thirdly, postsplenectomy sepsis can occur many years after splenectomy and, as Frank and Neu[8] suggest, studies with short follow-up may underestimate its frequency. Lastly, the incidence of sepsis varies with age, underlying disease process and the indication for splenectomy so to be useful any individual study must stratify for these variables.

O'Neal and McDonald[9] observed 256 adult splenectomy patients for an average of 45 months and found that 2·7 per cent developed postsplenectomy sepsis; they estimated that death from sepsis in these asplenic adults was 540 times as prevalent as death due to sepsis in the population at large. A comparable incidence of postsplenectomy infection was found by Hays *et al.*[10] in a population of 234 lymphoma patients who had undergone splenectomy as part of staging laparotomy. Over a mean surveillance period of 3·8 years there were four episodes of bacterial sepsis with positive blood cultures (1·7 per cent chance of sepsis), despite the fact that 83 per cent of the patients had received pneumococcal vaccination and 74 per cent had received prophylactic antibiotics.

Green *et al.*[11] however suggest that postsplenectomy sepsis is more common. They followed 144 postsplenectomy patients for an average of 61 months; 9 per cent developed major sepsis requiring hospitalization and 30 per cent developed minor septic complications. In contrast, Chaikof and McCabe[12] found that postsplenectomy sepsis was very uncommon. They reviewed 776 splenectomized patients over a mean follow-up period of 8·4 years. The incidence of fatal OPSI in their series was 3·7 per cent for children and 0·3 per cent for adults. This incidence seems low compared with some similar studies but Strauch[13] points out that the average age of adults in this series was 57 years and 127 adults in this series were lost to follow-up. These factors may explain the apparent low incidence of sepsis in this study.

Schwartz *et al.*[14] reviewed 193 postsplenectomy adults who were otherwise healthy with follow-up averaging 5·6 years. In this series the risk of serious infection (requiring hospitalization) varied with the indication for splenectomy. The overall rate of infection was 7·1 infections per 100 person-years of follow-up.

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The incidence (per 100 person-years) for the different splenectomy indications was: trauma, 3·3; primary splenic disease, 4·0; haematological diseases, 6·5; incidental to abdominal surgery for cancer, 16·6; and incidental to other forms of abdominal surgery, 9.6. Platt[15] considered this study valuable as it is free from bias, has nearly complete follow-up, and 'The low observed rate does not contradict reports of excess risk of pneumococcal sepsis after splenectomy, but does suggest that the absolute increase in attack rates is not great.'

Another approach to assess postsplenectomy infection was that of Robinette and Fraumeni[16]. They followed 740 servicemen, splenectomized for trauma in the 1939–45 war and demonstrated a significantly increased mortality rate from pneumonia and heart disease in these patients compared with individuals having intact spleens.

Despite the problems discussed above, multistudy reviews of OPSI do have the advantage of large numbers of patients. One such review is that of Singer[2] who reviewed 2795 postsplenectomy patients (from 24 series) and found that the overall incidence of sepsis was 4·2 per cent with an overall mortality rate of 2·5 per cent. As in the study of Schwartz *et al.*[14], risk varied with the indication for splenectomy; for the 921 patients who underwent splenectomy for trauma or incidental to other surgery, the incidence was 1·6 per cent and the mortality rate was 0·7 per cent.

Another review of 3430 collected cases[8] in 1981 assessed splenectomized patients under 17 years of age, and found an overall incidence of infection of 5 per cent. The highest incidence was in patients with congenital or acquired anaemias, portal hypertension, or lymphoreticular tumours. Overall for adults and children combined, sepsis occurred in 3·9 per cent with a mortality rate of 2·4 per cent. In a multistudy review by Ellison and Fabri[1] an overall incidence of postsplenectomy sepsis of 3·8 per cent was found; for paediatric patients the incidence was 4 per cent and the mortality rate was 1·8 per cent, while in adults the corresponding values were 1·9 per cent and 1·1 per cent respectively. Overall they concluded that the patients had a 40-fold increased risk of infection and a 17-fold increased risk of fatal sepsis.

What other factors influence the risk of postsplenectomy infection?

In some instances factors other than splenectomy seem to be more important in altering the risk of sepsis[13,17–19]. The risk of sepsis varies with the indication for splenectomy and in some circumstances splenectomy *per se* has a lesser part in predisposing to sepsis than the underlying disease. This is particularly true for patients with Hodgkin's disease. Donaldson *et al.*[20] in an assessment of 181 Hodgkin's patients, about half of whom had had splenectomy, could find no difference in infection or mortality rates between the two groups. Similarly, Keel and Bennett[21] compared 56 splenectomized patients with Hodgkin's disease with 28 non-splenectomized patients also with Hodgkin's disease. They found that for stage 2 and 3 disease splenectomy *per se* did not increase the risk of infection, and that the use of chemotherapy was a more important predisposing factor.

Whatever the relative importance of splenectomy *per se* compared with the underlying disease process, postsplenectomy patients are at an increased risk of sepsis. Balfanz *et al.*[22] point out that while the incidence of postsplenectomy infection is low, its mortality is high, making it a problem of major concern. Ellison and Fabri[1] state that 'Postsplenectomy sepsis in the adult having splenectomy for injury seems to be a rare event for which there is not sufficient solid evidence to establish an exact risk.'

Does splenectomy alter the susceptibility to infection in experimental animals?

Coil *et al.*[23] in a prospective study, showed that splenectomized mice were more susceptible to pneumococcal infection than intact controls, while Leung *et al.*[24] showed asplenic rats were more susceptible to *Pneumococcus* than controls. Similar results have also been found with susceptibility to coliform or *Haemophilus influenzae* infections[25], although Loggie and Hinchey[18] found that survival of mice after meningococcal challenge was similar in control and asplenic animals.

When does infection occur relative to splenectomy?

Fatal sepsis has been reported up to 30 years after splenectomy[1], but Schwartz *et al.*[14] found that most septic events occurred in the first year after operation. Similarly, Ellison and Fabri[1] found that 20 per cent of cases of fatal sepsis occur in the first 6 months after splenectomy and 60 per cent occur within 2 years. They also point out that the shorter the interval between splenectomy and sepsis, the greater the risk of mortality. A different perspective has, however, been put forward by Van Wych[6]. In his collection of 55 cases of OPSI less than 30 per cent occurred within 3 years of splenectomy.

Which age-group is at most risk from postsplenectomy sepsis?

The problem of postsplenectomy infection was first recognized in children and most series demonstrate a higher incidence in children than in adults. For example, Ellison and Fabri[1] found that postsplenectomy sepsis affected children twice as often as adults regardless of the reason for splenectomy, and that children also had a higher risk of mortality. A similarly increased risk in children was also described by Chaikof and McCabe[12] who found an 11-fold increase in risk of postsplenectomy infection in children compared with adults (incidence of 3·8 *versus* 0·3). Ellison and Fabri[1] also highlight the fact that the mortality rate is higher in children, concluding that postsplenectomy sepsis is fatal in over 50 per cent of paediatric cases but in less than one-third of adult cases.

The causative organisms in postsplenectomy sepsis

According to Ellison and Fabri[1] over 50 per cent of cases of postsplenectomy sepsis involve pneumococcal infection, other bacteria involved in descending order of frequency being *H. influenzae*, *Neisseria meningitidis*, β-haemolytic streptococci, *Escherichia coli* and *Pseudomonas* species Brigden[26] stressed that the encapsulated *Pneumococcus*, *Meningococcus* and *Haemophilus* species are the most frequently involved bacteria, a finding confirmed by other investigators[27]. It is also apparent that certain subtypes of the encapsulated organisms are more frequently involved. Gopal and Bisno[28] suggest that a limited number of pneumococcal serotypes predominate in postsplenectomy sepsis, in particular type 12, while Kafidi and Rotschafer[29] indicate that virtually all invasive *H. influenzae* disease occurring in the asplenic host is due to *H. influenzae* type b, and that most *N. meningitidis* infection results from groups A, B, C, Y and W135.

There are anecdotal reports of other organisms causing fulminating postsplenectomy infection, including *N. gonorrhoeae*[30], DF-2 bacterium[31], *Babesia* species[8], as well as cytomegalovirus[5], herpes[32] and influenza virus[33]. In addition, the Papua New Guinea Splenic Injury Group[34] indicate that splenectomy predisposes to malaria.

How does splenectomy alter the immune system and how effective are vaccines in preventing postsplenectomy infection?

How does removal of the spleen alter immune function?

In 1985 Brigden[26] stated that 'The mechanisms of defence against pneumococcal infection in humans are complex and include: the presence of adequate numbers of leucocytes, the action of type-specific antibody, the state of the host's reticuloendothelial system, the host's underlying illness, and medications given as therapy.' The spleen plays an important part in these defences and Ellison and Fabri[1] identified three components of the reticuloendothelial function of the spleen.

Phagocytosis and clearance of micro-organisms. Several aspects of phagocytosis and clearance of organisms are altered by splenectomy. Splenectomized rats have significantly impaired clearance of *Pneumococcus* compared with normal animals, and this is probably because the liver can only remove well opsonized bacteria from the blood, poorly opsonized bacteria being cleared only by the spleen[35]. Delayed type hypersensitivity reaction to *Bacillus* Calmette-Guérin vaccine in animals is reduced after splenectomy[36], as is amplifier T cell activity[37] and the production of memory cells[38]. The spleen also removes parasites, such as malarial organisms, from red blood cells and, as a consequence, splenectomy may reduce the host's defences[34].

Elaboration of a specific immune response. After exposure to an antigen the IgM antibody response is initiated in the white pulp of the spleen and after splenectomy antibody production and, therefore, opsonization of bacteria are likely to be reduced[8]. Frank and Neu[8] point out that encapsulated organisms must be opsonized before phagocytosis can occur. As a result there are two major reasons for reduced clearance of bacteria from the blood after splenectomy. Firstly, asplenic patients lack the splenic phagocytes capable of clearing bacteria coated with only small amounts of immunoglobulin and, secondly, they are unable to mount a sufficient antibody response to enable liver macrophages to overcome this defect[29,39]. Sullivan *et al.*[40] in 1978 also showed that after splenectomy the antibody subclass produced in response to pneumococcal vaccine did not switch appropriately from the initial IgM response to the later IgG response, as seen in normal individuals.

The production of opsonins. Eichner[41] discusses two proteins that the spleen produces which serve as opsonins: tuftsin, a tetrapeptide that promotes phagocytosis in polymorphonuclear leucocytes, and properdin, a vital component of the alternative complement pathway. Levels of both are reduced immediately after splenectomy and tuftsin deficiency has been noted up to 20 years later[8].

It was thought that deficiency of the alternative complement pathway, due to lack of properdin, might play a part in increasing the incidence of infection with encapsulated organisms after splenectomy[8]. However, this now seems unlikely as serum from asplenic patients will opsonize pneumococci as well as serum from normal patients[42], and Nielson *et al.*[43] after measuring complement titres in 85 splenectomized patients could not detect any major deficiencies. In addition, Hosea[38] states that 'The complement system has so much reserve that only after 99 per cent depletion of serum C3 are severe opsonic defects noted.' Thus it is probably not a primary defect in the complement system which predisposes to OPSI.

How effective are vaccines in preventing postsplenectomy infection?

Vaccine availability: Pneumococcal vaccine. Several vaccines against *S. pneumoniae* were evaluated in the 1920s but were abandoned when effective antibiotics became available. The current pneumococcal vaccine, Pneumovax-23 (Merck Sharp and Dohme, West Point, Pennsylvania, USA), consists of a mixture of purified capsular polysaccharides from 23 pneumococcal subtypes. Initial studies were conducted on healthy individuals with intact spleens[44,45] but more recently pneumococcal vaccine has been extensively studied in patients undergoing splenectomy.

Haemophilus vaccine. The *H. influenzae* vaccine was also first tested in populations of healthy individuals with intact spleens but unlike the pneumococcal vaccine it has not been extensively assessed in patients undergoing splenectomy Kafidi and Rotschafer[29] describe the two currently available vaccines and Peltola *et al.*[46] have demonstrated the effectiveness of *H influenzae* vaccination in a series of 50000 normal children.

Meningococcal vaccine. Kafidi and Rotschafer[29] describe a vaccine for *N. meningitidis* groups A and C which has been used for more than 10 years, but again most trials have been in healthy subjects and few series have tested its efficacy in patients undergoing splenectomy.

Antibody responses to vaccines. Some studies indicate that there is a decrease in antibody response to capsular polysaccharide vaccination after splenectomy[47] while others indicate that splenectomy does not alter antibody responsiveness[44,45]. A number of factors account for this conflict. Firstly, there is an individual variation in antibody response to vaccines; secondly, the different serotypes of vaccine induce different rates and magnitudes of antibody response; and lastly, some antibody assays are more sensitive than others[48–53].

Does splenectomy reduce the antibody response to capsular polysaccharide vaccination? The usual response of a healthy individual to pneumococcal vaccine is described as a twofold increase in type-specific antibody over a 2–3 week period[26]. In view of the changes in the immune system that occur following splenectomy it would be reasonable to expect postsplenectomy pneumococcal vaccination to be less effective than vaccination before the spleen is removed, and this is supported by the study by Di Padova *et al.*[54]. They showed that patients without spleens have an adequate early phase IgG response to pneumococcal vaccination at 7 days, and suggest that this response may be mediated by lymph nodes. However, they found that the mitogen-stimulated late phase response to pneumococcal vaccine at 21 days was impaired in asplenic patients. This finding, that the spleen has a central role in the production of the late phase antibody, confirms other reports[6,47,55] that splenectomy is associated with both a persistent deficiency of circulating B cells capable of synthesizing antipneumococcal capsular antibody and reduced IgM and IgG synthesis in peripheral blood mononuclear cells. As a result, a number of authors suggest that vaccines should be given before operation whenever possible[6,47,48,55–60]. Splenec tomy has also been shown to reduce the response to other vaccines, including *E. coli*[49].

Although most studies support the contention that pneumococcal vaccine will induce the greatest antibody response if given before splenectomy this is not to say that the reduced antibody response following vaccination performed after splenectomy will not offer some protection from sepsis. Although Perkins *et al.*[50] concede that the antibody level achieved in asplenic patients will be less than 50 per cent of that achieved in intact individuals, they suggest that the resulting antibody levels are still 'protective in most cases'.

A minority of reports conclude that splenectomy does not reduce the antibody response to capsular polysaccharide vaccination. For example, Dawes *et al.*[53] found no significant difference in antibody response to pneumococcal vaccine in rats that had undergone splenectomy, sham operation, hemisplenectomy or splenectomy with autotransplantation. Caplan *et al*[61] studied 16 patients having splenectomy for trauma and ten intact controls and concluded that if pneumococcal vaccination was administered within 72 h of operation the antibody response was not impaired. Addiego *et al.*[62] also found that untreated Hodgkin's disease patients had a similar antibody response to pneumococcal vaccination irrespective of whether the vaccine was given before or after splenectomy, and Siber *et al.*[63] found that the antibody response to pneumococcal, meningococcal and *H. influenzae* vaccines in Hodgkin's disease patients was not affected by the timing of immunization relative to splenectomy. Oldfield *et al.*[64] also came to a similar conclusion in a study comparing 21 asplenic patients with 12 controls.

How long does the antibody response to polysaccharide vaccination last? Borgono *et al.*[65] studied intact adults and showed that there was only a minor decline in antibody titre 13 months after vaccination. In a longer follow-up study in intact individuals Vela *et al.*[66] found that adults had a 50 per cent decline in pneumococcal vaccine-induced antibody titre at 3 years while children showed a similar decline after only 21 months.

Weibel *et al.*[67] found only a slight decline in antibody titres to pneumococcal vaccine 20 months after vaccination. In addition, Giebink *et al*[68] studied vaccinated asplenic children and found significant variations in the rates of decline in titre for the different capsular subtypes. Other studies indicate that antipneumococcal antibodies induced by vaccination disappear more rapidly in asplenics and in immunosuppressed and lymphoma patients[63] than in controls. It appears that the rate of decline of IgM is more rapid in asplenics than in intact controls while the IgG response declines equally in both groups[69,70].

For the meningococcal and *Haemophilus* vaccines, information on the rate of decline of vaccine induced antibody is only available for subjects with intact spleens. Kayhty *et al.*[71,72] followed several thousand healthy children vaccinated against *H. influenzae*. In infants aged less than 18 months protective titres lasted less than 6 months while in the infants aged over 18 months protective titres persisted for up to 3 years.

Vaccine responses in children. Some studies place the efficacy of pneumococcal vaccines for young children in doubt. For example, Hilleman *et al.*[73] found that intact children less than 2 years of age had a diminished antibody response to pneumococcal vaccine when compared with older children. Francke and Neu[8] came to the same conclusion and suggested that children probably do not respond adequately to any capsular vaccines until 4 years of age This latter contention is disputed by Cowan *et al.*[74] who demonstrated that some pneumococcal polysaccharide types resulted in a significant antibody response as early as 3 months of age. Furthermore, Aaberge and Heier[69] conclude that splenectomized children as old as 15 years of age have a reduced antibody response to pneumococcal vaccination when compared with the adult response.

Despite the apparent diminished antibody response to vaccination in children, some clinicians feel that it is still worth giving the pneumococcal vaccine on the off-chance that the patient gains some protection. Ammann[75] suggests that pneumococcal immunization of patients under 2 years of age is probably not harmful and could result in protection. On the other hand, Granoff[76] suggests that there is not enough information to recommend pneumococcal vaccination for children under 2 years of age. Data concerning the use of other vaccines in children are sparse but Peltola *et al.*[46] conclude that, for *H. influenzae* vaccine, the earliest age at which an adequate antibody titre can be induced is 18 months.

Other factors likely to influence the antibody response to vaccination. Many studies suggest that the underlying disease and/or its treatment may affect the antibody response to vaccination as least as much as splenectomy *per se*. Pedessen *et al.*[77] found that the antibody response to pneumococcal vaccine in 67 splenectomized patients with benign disease was not significantly different from that of 12 healthy controls with intact spleens; in comparison, five untreated splenectomized adults with malignant disease and 11 splenectomized adults receiving immunosuppressive therapy showed a significantly reduced antibody response to the vaccine. Similarly, Shildt *et al.*[78] found that patients with lymphoma treated with chemotherapy had a comparatively poor antibody response to pneumococcal vaccination. From another perspective, Shapiro and Clemens[79] conducted a case control study into the protective effect of pneumococcal vaccine and concluded that the vaccine had an overall protective efficacy of 67 per cent, while in the severely immunocompromised patients protection was almost nil.

Similar conclusions have been drawn for meningococcal vaccination. Ruben *et al.*[80] tested a bivalent meningococcal vaccine on 22 asplenic patients and 15 controls. Those whose spleens had been removed for trauma, non-lymphoid tumours or idiopathic thrombocytopenic purpura had antibody responses similar to healthy controls. However, the antibody response was reduced in patients who underwent splenectomy for lymphoid tumours, and again the IgM response was more affected than the IgG response.

It is difficult to separate the influence on the immune system of the presence of a lymphoid tumour *per se* from the effect of immunosuppressive treatment, but it appears that immunosuppressive treatment is the more important. Donaldson *et al.*[81] indicate that 'Although Hodgkin's disease may have major effects on cellular immune mechanisms, little evidence supports the theory that the disease significantly alters the ability of individuals to develop adequate humoral immunity.' They found that children who were immunized at the time of initial diagnosis, before splenectomy and subsequent immunosuppressive treatment, had a significantly better response to vaccination than children who had undergone staging and treatment. In addition, Addiego *et al.*[62] showed that pneumococcal vaccination induced a significant antibody response in virtually all patients with Hodgkin's disease, either before or after splenectomy, providing they had not commenced immunosuppressive treatment. The antibody response to vaccination was significantly reduced if chemotherapy was commenced within 10 days of immunization.

Another factor influencing the response to vaccination is genetic make-up. Ambrosino *et al.*[82] found that individuals with the genetic marker of the IgG-2 subclass had an enhanced antibody response to *H. influenzae* and meningococcal vaccines when compared with marker-negative individuals. Genetic make-up may also influence an individual's antibody response to other vaccines[52].

Neither anaesthesia nor surgery appears to influence the antibody response to vaccination. In rats vaccination immediately after anaesthesia and surgery does not reduce antibody responsiveness[83], while in man the antibody response to pneumococcal vaccine is not impaired in patients with healed traumatized spleens[70].

Do polysaccharide vaccines protect patients from pneumococcal infection? Several studies suggest that polysaccharide vaccination, in addition to inducing an antibody response, also provides *in vivo* protection from bacterial disease. For instance, Scher *et al.*[35] immunized rats with pneumococcal vaccine 2 weeks after splenectomy and found that when inoculated with *Pneumococcus* they had significantly better pneumococcal clearance than non-immunized rats. Other investigators, also using animal models, have reached similar conclusions[53], and *in vivo* human studies also show that vaccines have a protective effect. For example, Bolan *et al.*[84] found that pneumococcal vaccine effectively prevented bacteraemic pneumococcal disease in asplenic subjects providing they were fully immuno competent.

On the other hand there are a number of reports of vaccine failure. The fact that capsular polysaccharide vaccines do not eliminate postsplenectomy sepsis (rather they merely reduce its incidence) is highlighted by reports documenting sepsis despite the use of vaccination and/or prophylactic antibiotics[85–88].

Ellison and Fabri[1] point out that half the organisms causing postsplenectomy sepsis are not pneumococci and that at least 20 per cent of pneumococcal subtypes are not covered by the available vaccine. They also suggest that the incidence of various antigenic types in pneumococcal infection is changing and, as a result, the protection offered by any particular vaccine may be variable. Brigden[26] also highlights the fact that the 23-valent pneumococcal vaccine does not cover all subtypes of bacteraemic pneumococcal disease encountered in North America, and Schlaeffer *et al.*[85], after reviewing 59 cases of pneumococcal bacteraemia in patients who had received 14-valent pneumococcal vaccine, found that 32 per cent of strains of pneumococci responsible for sepsis were not present in the vaccine

There are also reports of vaccine-type pneumococcal sepsis occurring in vaccinated splenectomized patients[89]. Zarrabi and Rosner[90] studied pneumococcal sepsis and meningitis in recipients of pneumococcal vaccine and found that 21 out of 33 pneumococcal isolates in splenectomized patients were subtypes included in the vaccine. Further, 14 out of 22 pneumococcal isolates in patients who had intact spleens were vaccine serotypes.

Vaccine side-effects. In general, serious side-effects of pneumococcal vaccine are rare, with only five anaphylactic reactions per million doses administered[91]. Minor side-effects, however, are common and the Advisory Committee for Immunization Practices[91] found that half the patients who received the 14-valent pneumococcal vaccine developed side-effects, including erythema, mild pain at the injection site or transient fever[61] One other unusual complication is important; patients with idiopathic thrombocytopenic purpura may rarely find that their disease is exacerbated by immunization with pneumococcal vaccine[26].

The *Haemophilus* and meningococcal vaccinations also appear to be safe[29] and all three vaccines can safely be given together in a single dose without loss of immunogenicity[92]

Booster vaccinations. Repeat or 'booster' doses of pneumococcal vaccine are not recommended. After a second dose of pneumococcal vaccine side-effects and severe reactions are common[29,65,91], and it has also been shown that booster doses do not result in a substantial increase in serum IgG or IgM levels[65,73]. In addition, the risk of postsplenectomy infection is greatest in the years immediately after splenectomy and protective levels of antibody from one vaccination at the time of splenectomy should persist over this high-risk period[63,66,67,69]

A question that has arisen is whether patients previously immunized with a 14-valent pneumococcal vaccine should be reimmunized with the 23-valent vaccine? The American Academy of Pediatrics does not recommend this[93] because of the increased risk of adverse reaction. The Centers for Disease Control[94] also discourage this practice on the basis that the modest increase in coverage does not warrant the increased risk of possible adverse reaction. In contrast, Kafidi and Rotschafer[29] suggest that revaccination with the tetravalent meningococcal vaccine is indicated in children under 4 years of age.

Recommendations regarding the use of vaccines. In the light of the information presented above it seems reasonable to offer all splenectomized patients vaccination with pneumococcal, meningococcal and *H. influenzae* vaccines[8]. Patients undergoing elective splenectomy should ideally receive the vaccines before surgery[55], and patients with lymphoid tumours may gain some benefit if they receive these vaccines before therapy[78]. All three vaccinations can be given together[92] but they should not be administered at the same time as chemotherapy or other immunosuppressive treatment[78].

Patients having emergency splenectomy for trauma should be vaccinated as soon as possible after surgery[15,56].

Are other methods of prophylaxis worthwhile?

Other methods of preventing postsplenectomy infection include splenic salvage, autotransplantation and prophylactic antibiotic administration.

Splenic salvage

Although conservative management is the norm in many cases of childhood splenic trauma, it became unpopular earlier this century in adults as total splenectomy became safer. Recently, however, splenic salvage in adults has been reconsidered and many clinicians have used splenic conservation successfully. For instance, the Papua New Guinea Splenic Injury Study Group[34] describe a series of 205 adult patients with ruptured spleens from several hospitals. Initial non-operative management was attempted in 137 of these cases, and was successful in 80 per cent. King *et al.*[95] also describe a successful management plan for splenic trauma favouring non-operative treatment.

Conservation of part of the spleen has also been used effectively but estimates of the amount of spleen that needs to remain to protect a patient from infection vary. Ellison and Fabri[1] indicate that at least one-third of the splenic mass must be conserved to maintain splenic immune function. They also suggest that ligation of the splenic artery and salvage of the spleen via collateral blood supply, as used in animal models, reduces splenic blood flow to such a degree that the immunological protection offered by the spleen is lost. In contrast, Greco and Alvarez[96] have shown in rats that as much as 80 per cent of the spleen can be removed, and because the remnant undergoes hypertrophy, host protection against a subsequent pneumococcal challenge is preserved.

Whether small splenic remnants offer protection against infection is debated. Greco and Alvarez[96] suggest that partial splenectomy with conservation of even quite small portions of spleen attached to identifiable blood vessels yields significant protection from life-threatening sepsis. Similarly, Van Wyck *et al.*[97] have demonstrated an advantage of splenic remnant preservation over splenectomy in terms of antibody responsiveness Certainly conservation of the spleen is the ultimate prophylaxis for postsplenectomy infection and this approach should probably be used both in children and adults wherever possible[1].

Techniques of splenic salvage have been reviewed elsewhere[98]. For minor lacerations or capsular tears local pressure and the application of a topical haemostatic agent is usually successful[99]. More major injuries usually require some form of splenorrhaphy and this can be accomplished using simple suture, suture with Teflon® (du Pont) buttresses or the incorporation of an omental patch[98]. 'Cocooning' the spleen in a polyglycolic acid mesh has also been described[100].

Splenic autotransplantation

Four techniques of splenic autotransplantation have been used: into the abdominal wall, into an omental pouch, intraperitoneal injection and intrahepatic injection Ellison and Fabri[1] reviewed the literature on autotransplantation in 1983 and concluded that functioning splenic tissue could be produced in experimental animals by all of these techniques except intrahepatic injection. Although autotransplantation does provide a method for preserving some splenic function they concluded that it was inferior to partial splenectomy.

Many investigators have assessed the potential of autotransplantation in animal models. Moxon *et al.*[25] found that splenic autotransplantation reduced the incidence of *H. influenzae* meningitis in asplenic rats, while Likhite[101] also showed that subcutaneous splenic fragments gave some protection from pneumococcal infection in mice.

However other investigators have reservations. Scher *et al.*[35] indicate that while splenic autotransplantation does enable asplenic rats to develop a better antibody response to sheep erythrocytes it does not provide protection against pneumococcal infection. In accord with these observations Kiroff *et al.*[58] assessed the degree of ectopic splenic regrowth isotopically and after measuring the antibody response to pneumococcal vaccine and found that there was no difference in responsiveness between patients with splenosis and those without.

Summing up this problem, Greco and Alvarez[96] conclude that splenic autotransplantation 'remains an experimental procedure which cannot be reliably performed in humans if one's intent is to protect the recipient against infection.'

Antibiotic prophylaxis

Antibiotic prophylaxis has become the norm for selected postsplenectomy patients and is recommended by a number of clinicians. For instance, Franck and Neu[8] suggest using antibiotic prophylaxis in postsplenectomy patients with the following indications: low initial levels of antibody to pneumococci or a high risk of exposure to pneumococcal infection, and in those undergoing chemotherapy for malignancy or who are aged less than 5 years. Ammann and Diamond[102] recommend continuous antibiotic prophylaxis for children from the time of splenectomy up to the age of 5 years, while Ellison and Fabri[1] suggest that antibiotics are most important in the 2–3 years after splenectomy.

However, there are reports of prophylactic antibiotics failing to prevent infection[87,88], and some animal studies also cast doubt on their efficacy. For example, Scher *et al* [35] found that prophylactic penicillin does not increase the clearance of *Pneumococcus* from the blood of asplenic rats. Another problem with antibiotic prophylaxis is poor patient compliance[8].

Traditionally penicillin has been the prophylactic antibiotic of choice[1,7] However, the use of other antibiotics has been suggested and Singer[2] points out that half of the septic episodes in asplenic patients are due to organisms that are not sensitive to penicillin On this basis Frank and Neu[8] recommend amoxycillin as this is also effective against *H. influenzae.* On the other hand, Fillner (see Leonard *et al.*[7]) does not recommend amoxycillin for prophylaxis because it is more expensive than penicillin and because it has twice the incidence of allergic rashes. Kyong and Reines[103] conclude that the morbidity and expense of long-term ampicillin probably outweigh the benefits of its use

Prompt recognition and treatment of infection may be at least as useful as prophylactic antibiotics. Both Van Wyck[97] and Kyong and Reines[103] feel that a most useful way of preventing infection is to attend quickly to any febrile illness in an asplenic patient. This is further supported by the contention of Gullstrant *et al.*[104] that penicillin is more effective when given early after a pneumococcal challenge than when given late, and many clinicians give the patient a supply of ampicillin to use at the first sign of a respiratory illness or fever[19].

Browder *et al.*[105] used glucan, an immunostimulant, in splenectomized mice to increase phagocytic function, and observed a significant increase in survival following a pneumococcal challenge. There are, however, no human data available at present regarding glucan.

Conclusions

The primary aim of this review was to answer three questions.

What are the infectious consequences of splenectomy?

Postsplenectomy sepsis is rare following splenectomy for trauma and uncommon following splenectomy for other reasons. The patients most at risk are children and those splenectomized for lymphoreticular malignancy. The causative organism in about 50 per cent of cases is *S. pneumoniae* and more than 50 per cent of cases of OPSI occur within 2 years of splenectomy. However, *Meningococcus*, *Haemophilus* and other bacteria are also involved, and splenectomy may also increase the morbidity of some parasitic and viral infections.

How does removal of the spleen alter the immune system, and how effective are vaccines in preventing postsplenectomy infection?

Splenectomy reduces phagocytosis and clearance of micro-organisms, the elaboration of a specific immune response and the production of splenic opsonins. Vaccines are available against *Pneumococcus*, *Meningococcus* and *H. influenzae*. Studies of the antibody response to them have shown varying results but, overall, splenectomy appears to reduce antibody responsiveness. Other factors also known to reduce the response to vaccination include: age less than 3 years, haematological malignancy, immunosuppressive therapy and genetic profile. Surgery and/or anaesthesia do not appear to diminish responsiveness

In general, capsular polysaccharide vaccines appear to be effective in reducing the incidence of postsplenectomy infection although there are numerous reports of sepsis despite vaccination. Probably the optimal regimen is vaccination with pneumococcal, meningococcal and *H influenzae* vaccines as long as possible before operation for patients undergoing elective splenectomy, and for patients receiving immunosuppressive therapy the vaccine should be given between courses of treatment. Although responsiveness may be reduced in patients vaccinated after splenectomy for trauma, they should still receive vaccine as soon as possible after operation as they are likely to develop a protective response.

Serious side-effects following a single vaccination are rare but are common following a second or booster dose.

Are other methods of prophylaxis worthwhile?

In children splenic salvage is an accepted technique for preventing postsplenectomy infection. In adults conservative management of splenic trauma is emerging as a useful technique and should be considered whenever it can be accomplished safely.

Although splenic autotransplantation may have potential, there is insufficient evidence in humans for the technique to be widely promoted at present. Prophylactic penicillin should be used in addition to vaccination in asplenic patients at especially high risk of infection, notably children aged less than 5 years and immunosuppressed patients For other patients, in addition to vaccination, education regarding the prompt recognition and treatment of infectious illnesses is probably more appropriate

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Gastrointestinal malignancy: rationale for adjuvant therapy using early postoperative intraperitoneal chemotherapy

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The treatment of gastrointestinal cancer and the prognosis of patients with this disease have changed very little over the past several decades. No screening tools have been developed which allow this disease to be surgically treated for cure at an early stage. None of the forms of adjuvant chemotherapy instituted in the months and years after surgical resection of cancer have been successful. We show that resection site recurrence and spread of disease on the peritoneal surfaces are the most common sites for surgical treatment failure. By changing the route of administration and the timing of chemotherapy, the efficacy of drugs now routinely employed in gastrointestinal cancer can be markedly improved. Our early studies suggest that there is a definite change in the natural history of these malignancies when intraperitoneal chemotherapy is administered immediately after surgery. The pharmacology and physiology of drug delivery in the immediate postoperative period are explored. Toxicity studies have been performed in a series of treatment protocols already in use. These protocols need to be subjected to randomized controlled trials in the near future.

Keywords: Gastrointestinal cancer, intraperitoneal chemotherapy

The three most common causes of malignancy of the digestive system, adenocarcinoma of the large bowel, stomach and pancreas, will affect approximately 200 000 patients in the USA this year[1]. While gastric malignancy has become less common, both colorectal and pancreatic malignancies are increasing in frequency[2], in Europe as well as in the USA[3]. Of newly diagnosed patients with such malignancy, far fewer than half will be alive and free of disease after 5 years[4–6]. The factors responsible for this poor outlook are discussed, together with the rationale for a new adjuvant treatment, namely early postoperative intraperitoneal chemotherapy. This treatment may modify the natural history of gastrointestinal cancer by reducing cancer spread at the resection site and on peritoneal surfaces. We suggest that this novel addition to the postoperative care of gastrointestinal cancer patients may have important although limited goals. The rationale for this approach comes from a study of the patterns of recurrence.

Patterns of recurrence

Surgical treatment failure with gastric cancer

Gastric cancer is often advanced at presentation[7], metastases may arise at an early stage of the disease[8] and the malignancy may be multifocal[9,10]. After curative surgery the 5-year survival rate in the USA is less than 20 per cent[11]. The probable reasons for this low survival rate are the high operative mortality rate of approximately 10 per cent and the high rate of local recurrence. Following surgical treatment, very few patients have recurrence confined to the liver or lung. Accurate autopsy series have consistently shown recurrent intra-abdominal disease in up to 75 per cent of patients[11–19]. Clearly, a major problem with gastric cancer is the frequent finding of local/regional recurrence.

The Japanese, who see many more patients with gastric cancer than surgeons in either Europe or the USA, have approached the problem with extensive data gathering. In conjunction with gastrointestinal endoscopists and pathologists, they have undertaken an aggressive surgical approach, with extensive anatomical documentation of extent of disease in each patient[20]. The result has been an increase in the operability rate, a reduction in the operative mortality rate and an improved survival[21], especially when compared with series from Europe or the USA[15,22]. Interestingly, the early Japanese results in the 1940s were similar to contemporary results in Europe or the USA. Improvement in their results began after the unified approach used by all concerned in the management of patients with gastric cancer. This approach has been adopted by a British group who were able to demonstrate, on a smaller scale, similar improved results[23]. Despite the greatly improved (approximately 70 per cent) 5-year survival rate achieved by the Japanese, they still accept the need for adjuvant therapy in the management of gastric cancer[24].

Surgical treatment failure with pancreatic cancer

Pancreatic cancer shares features that are characteristic of gastric neoplasms, such as advanced disease at presentation[5,25–28], multicentricity[29,30] and metastasis early in the disease[28,31]. Added to this is the fact that local recurrence is the most common site of disease recurrence with pancreatic cancer[32]. There is no doubt that some form of adjuvant therapy is indicated if any progress is to be made in the management of this condition.

The surgical approach to pancreatic cancer has been woefully inadequate. Despite surgery, over 95 per cent of patients will die of their disease within 5 years of diagnosis[33–36]. Surgical opinions have been divided over the most appropriate surgical therapy for this condition. Some authors have advocated palliative surgery only, as this therapy has been demonstrated to have fewer complications and a comparable median survival[37]. Other surgeons are undecided about how

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radical the surgery should be. Whipple's operation has been popular since its inception in 1935[38] and it has the advantage of removing the tumour without necessarily rendering the patient diabetic or prone to malabsorption. Total pancreatectomy avoids the need for a potentially troublesome anastomosis but may produce patients with a diabetic and metabolic state that is difficult to control[5,39]. Sindelar *et al.*[40] reviewed the literature on results of radical surgery for pancreatic cancer and found that the operative mortality for the Whipple procedure performed in 814 patients with this disease was 19·5 per cent compared with 22 per cent in 300 patients undergoing total pancreatectomy. Both groups had significant morbidity in at least half the patients. In the Whipple group, sepsis and fistula formation accounted for half of the complications, while sepsis and metabolic complications accounted for half of the complications in the total pancreatectomy group. Survival rates at 3 and 5 years were 13·1 and 8·1 per cent respectively in the Whipple group compared with 18·4 and 9·3 per cent in the total pancreatectomy group. It should be emphasized that these were not controlled comparative studies, but the comparison of published data from the literature.

Surgical treatment failure with colorectal cancer

This disease accounts for over half of the cases of gastrointestinal malignancy. Surgery alone is the current therapeutic option. As expected, there has been no major improvement in the overall 5-year survival rate in the last 40 years[41]. As with the other two gastrointestinal malignancies, the disease is often in an advanced state at presentation[42–44], with barely 20 per cent of patients having disease confined to the superficial layer of the bowel. Synchronous hepatic metastases may be present in approximately 15 per cent of patients[45–47].

Local/regional recurrence following surgery is a major problem with colorectal cancer, a fact that has been highlighted with respect to whether low anterior resections using a stapling device have higher recurrence rates than conventional techniques[48,49]. Local recurrence rates of up to 50 per cent have been documented in both rectal[50–52] and colonic cancer[52–58]. Clinical studies suggest that as many as one-third of all cases recur solely in the liver, although this has not been confirmed by the more accurate reoperative and autopsy series in which this figure is placed closer to 10 per cent[53,56,58]. In the series reported by Gunderson and colleagues, 74 per cent of all the patients who relapsed had either local–regional recurrence or peritoneal seedlings or both[58]. A review of collected reports in the literature in which 2565 cases of large bowel cancer were treated shows that of the 438 cases with recurrence, 42 per cent had a local component only, 27 per cent had a distant component only while the remaining patients had both local and distant recurrences[51,56,59–65].

Figure 1 is a schematic representation of recurrence typical of surgically treated gastrointestinal cancer. Patients will present with recurrent disease in the operative site, with peritoneal implants, with hepatic metastases, and with systemic metastases. An optimal adjuvant surgical therapy should be effective at all sites of recurrent disease, both local/regional and systemic. However, elimination of recurrence at a particular anatomical site may benefit a significant proportion of patients in terms of survival or quality of life.

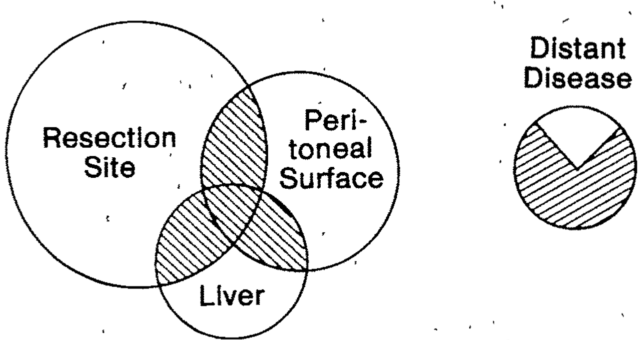

Figure 1 *Recurrence pattern in patients with gastrointestinal cancer. A combined recurrence (■) is more usual than isolated recurrence (□)*

Pathological indicators of patterns of recurrence of colorectal cancer

The routes of spread likely for an individual patient with gastrointestinal cancer are indicated by pathological studies of the primary tumour specimen. Penetration through the bowel wall is followed by circumferential growth of cancer. Intestinal obstruction is the eventual outcome. This results from tumour extension along transversely aligned lymphatic channels. Full thickness penetration of cancer through the bowel wall may result in peritoneal seeding, carcinomatous invasion of adjacent structures, or bowel perforation. Lymphatic spread does not usually occur until the bowel wall is penetrated by cancer[42,66] unless the tumour is poorly differentiated[43,67], in which case it can spread while still in the tip of an adenomatous polyp[68]. The more advanced the local disease, the more likely is both lymphatic[44,69] and haematogenous spread[70]. Haematogenous spread may occur directly through tumour emboli released into the portal vein or Batson's plexus. Haematogenous metastases may also occur via an indirect route, tumour cells passing from lymph nodes to the thoracic duct and to venous blood. Lymphatic spread is usually stepwise with involvement of the nodes closest to the lesion being followed by involvement of more distal nodes[71,72], but 'skip' metastases do occur[71,73], as does retrograde spread[74]. At the time of initial diagnosis, upwards of 20 per cent of patients may have evidence of haematogenous spread[75], and the histological finding of venous invasion in the primary tumour correlates well with the presence of haematogenous disease[76].

Despite curative gastrointestinal surgery, more than 5 per cent of patients will die from recurrent disease[77]. This recurrence follows 'removal' of the malignancy[78]. The possible mechanisms of surgical treatment failures have been outlined by Sugarbaker and colleagues[75]: (1) foci of neoplastic cells dislodged from the lateral margins of resection and lymphatic channels or present in venous blood may be disseminated as micrometastases on to peritoneal surfaces and into the resection site; (2) tumour cells may disseminate into veins before or at the time of surgery as a result of manipulation[79]; and (3) intraluminal tumour cells exfoliated at the site of bowel transection or on to mucosal margins may lead to anastomotic recurrence[80]. This last phenomenon may explain reports of anastomotic recurrence rates of up to 30 per cent[81–84], which can be reduced by using intraluminal irrigating solutions[85–87]. A recent review has covered this subject comprehensively[88]

A new hypothesis by which to understand the recurrence patterns of surgically treated gastrointestinal cancer is the fibrin entrapment hypothesis. This hypothesis separates the mechanisms by which recurrent cancer comes about into two groups 'tumour metastases' are viewed as a lymphatic or haematogenous dissemination that occurs before surgery but which is not recognized because of the small size of the malignant foci; 'tumour spread' is viewed as cancer dissemination that results from the inevitable trauma of the surgical removal of a gastrointestinal malignancy. Haematogenous spread can be prevented by gentle resection techniques and wide anatomical dissections. However, spread of tumour within the abdominal cavity into the resection site and on to peritoneal surfaces is unavoidable in patients with advanced tumours. Even though the tumour is removed with negative margins, tumour emboli from transected lymphatic channels, tumour emboli disrupted from narrow lateral margins of resection and tumour cells lost into the abdominal cavity will be trapped in the fibrin that occurs in the resection site and on abraded peritoneal surfaces. These tumour cells will be protected from host defences and systemic chemotherapy, causing a high incidence of intra-abdominal recurrence.

Systemic chemotherapy with or without radiation therapy

Gastric cancer

A review of the literature by MacDonald *et al.*[89] gives a comprehensive analysis of response rates for various single agent drugs used in trials of 14 or more patients. The response rate varies from zero with razoxane[90] to 36 per cent with doxorubicin[91]. Despite these response rates, the duration of response rarely exceeds a few months and complete responses are uncommon. Any response achieved with such therapy is often negated by the associated toxicity. This pessimistic experience contrasts with results from Japan where survival benefits have been reported with 5-fluorouracil (5-FU)[24]. Some concern should be expressed for some Japanese studies, as they appear to have dropped the control arm and make use of historical controls for comparison[19,92].

By combining various drugs, therapeutic synergism is anticipated Of the prospective studies using combinations, the Gastrointestinal Tumor Study Group study demonstrated a survival benefit[93]. Two other series[94,95] showed no survival benefit following adjuvant therapy. The British Stomach Cancer Group were unable to demonstrate survival benefits in patients treated with Mitomycin C and 5-FU after surgery compared with a surgery-only control group[96]. Other authors have used pharmacological manipulation of the chemotherapeutic drugs to improve response. For example, Machover *et al.* found that by adding folinic acid to 5-FU, response rates were improved[97] Other authors have used an oil base for the drugs in order to localize them to lymphatics and lymph nodes, again improving response rates[98]. Despite these manipulations, no significant survival benefit has been conferred when results are prospectively compared with those of surgery alone.

By combining radiotherapy and chemotherapy together, conflicting results have been achieved in gastric cancer patients. Some authors report responses[99,100] while others fail to demonstrate success with the method[101,102].

Pancreatic cancer

Untreated pancreatic cancer has a median survival of 3–4 months[36] and, as mentioned above, the majority of patients with pancreatic cancer have advanced disease. In many studies over 85 per cent of patients are unsuitable for curative resection. These patients are often nutritionally depleted and have a poor life expectancy. In the past, obtaining a histological diagnosis has often been difficult in a proportion of patients[103,104], although newer fine-needle cytology techniques improve the diagnostic rate[105]. As a result of these problems, studies investigating adjuvant chemotherapy for pancreatic cancer involve the use of drugs in patients where advanced disease is nearly always present.

As single agent therapy, 5-FU has been used in pancreas cancer. Davis *et al* reported the results from 129 patients treated with 5-FU by a variety of routes where the overall median survival was 4 months[106]. Survival was 6 months in the 25 patients receiving systemic 5-FU, while survival was 7 months in 21 patients receiving 5-FU in conjunction with radiotherapy. Oral 5-FU appears to be ineffective[107]. In 1979, the Gastrointestinal Tumor Study Group studied patients after surgery and compared patients treated with 5-FU with moderate dose radiotherapy (4000 cGy) or 5-FU with high dose radiotherapy (6000 cGy) with patients treated with 6000 cGy alone. Those patients treated with 5-FU and any type of radiotherapy survived longer than those treated with radiotherapy only (35 *versus* 18 weeks), whereas those treated with high dose radiotherapy and 5-FU survived longer than those treated with low dose radiotherapy and 5-FU (39 *versus* 31 weeks). However, this survival difference between the high and low dose radiotherapy groups was not maintained after 1 year[108]. An update of this study has shown that the median survival in the adjuvant treated group was 20 months compared with 11 months in the surgery-only group[109]. Projected 2-year survival was 42 per cent in the adjuvant group compared with 15 per cent in the surgery-only group.

Several combinations of drugs have been studied. The response rates vary from 7 to 48 per cent without the median survival being affected. An interesting development in chemotherapy for pancreatic cancer is the discovery of oestrogen receptors in pancreatic tumour tissue, suggesting a possible role for agents such as tamoxifen[110]. Initial reports in the Scandinavian literature have been encouraging[111] but the results of definitive studies are awaited.

In pancreatic cancer, the combination of these methods of treatment, with or without surgery, has resulted in some reports of improved survival[26,112–114]. However, it is clear that adjuvant chemotherapy does not necessarily confer a major advantage and there is a long way to go before significant progress is achieved.

Colorectal cancer

With colorectal cancer a large number of studies have been generated using adjuvant chemotherapy. Few of the difficulties outlined above with respect to pancreatic cancer are applicable to colorectal cancer: histological diagnosis is usually easier to obtain, the majority of patients will undergo resection, and at least 70 per cent of patients will undergo curative resection[115,116].

The use of single agents in adjuvant therapy has been investigated, with one early report of the use of intraperitoneal Thiotepa showing no advantage[117]. The Veterans Administration Group studied the use of 5-FU in patients with poor prognosis and in palliative surgery-only patients and were able to demonstrate a trend towards prolonged survival in the treatment groups: 33 *versus* 26 per cent in surgery-only controls at 7 years in poor prognosis patients, 38 *versus* 26 per cent for surgery-only controls at 18 months in palliative surgery-only patients[94]. These differences did not achieve statistical significance. Grage *et al* [118] confirmed this trend in a further study of 210 patients undergoing curative surgery for whom overall survival rates were 56 *versus* 50 per cent for controls at 5 years: but it was noted that in Dukes' C patients, prolongation of the disease-free interval just achieved statistical significance ($P = 0{\cdot}04$). A similar result was found in rectal cancer patients. This small benefit attributable to 5-FU has been reported consistently[119] Other studies have reported benefit with other single agents using historical controls, but prospective randomized studies invariably fail to demonstrate survival benefit using these drugs.

Several studies have examined the use of combination chemotherapy as an adjuvant to surgery. Although survival benefits are only infrequently demonstrated, the trend towards improved survival in patients with more advanced disease was seen. The NSABP study[120] showed that for colonic cancer patients treated with 5-FU, semustine and vincristine, the survival benefit achieved ($P = 0{\cdot}05$) was independent of Dukes' classification. As far as rectal cancer is concerned, the NSABP trial[121] reported increased disease-free survival in patients treated with chemotherapy following curative resection when compared with controls treated by surgery alone. In this study, patients with rectal cancer treated with surgery plus postoperative radiation therapy showed no survival advantage.

In colorectal cancer, some authors have reported benefit by combining the modalities, compared with surgery alone[122], while others have found that any benefit derived was confined to patients with advanced disease[91].

Patients with metastatic disease are usually excluded from these studies, but some authors have attempted to prevent hepatic secondaries with chemotherapy. Taylor and associates reported encouraging results with this method where 5-FU was perfused via a portal vein catheter[123]. Updates of this work continue to be favourable[124] and a recent presentation by Kemeny and associates[125] notes the advantage of giving 5-FUdr via the hepatic artery when compared with intravenous use in patients with metastatic hepatic disease. However, intra-arterial 5-FUdr may give rise to sclerosing cholangitis[126].

As with the other gastrointestinal malignancies, encouraging response rates with gross disease have not been translated into improved survival for the group as a whole. Possibly, the proportion of cancer cells killed with systemic chemotherapy is too small to translate into significant differences in survival. Modest prolongations of disease-free survival reflect some reduction in tumour burden, but these weak effects are incapable of translating into overall survival benefits. It seems reasonable to propose that when tumour bulk is minimal, such as following resection of Dukes' A or B tumours, adjuvant therapy would be at its most effective. Unfortunately, these beneficial effects are statistically not appreciated because a major proportion of such patients survive with surgery alone. The successes are obscured by the large number of patients not needing adjuvant therapy. The much poorer survival of patients with 'advanced' primary tumour may allow weak effects to be detected in well conducted clinical trials.

In summary, we suggest that the population of patients who might benefit most from weak effects are those in whom the effects are most difficult to detect in a clinical trial. Studies have consistently shown that if systemic adjuvant therapy is effective at all it is in those patients with the more advanced primary disease rather than those with lymph node negative primary tumour.

Early postoperative intraperitoneal chemotherapy: a new adjuvant treatment

Intraperitoneal chemotherapy has been used, with limited success, for at least 30 years[125,127,128]. The pharmacodynamics of intraperitoneal chemotherapy have been documented by Dedrick *et al.*[129]. The most fundamental observation in their pharmacokinetic modelling studies was that the peritoneal clearance of a drug was inversely proportional to the square root of its molecular weight. Thus, large molecules (like many cancer chemotherapy agents) take longer to clear from the peritoneal cavity than smaller ones. This rule is true as long as the compound is not highly lipid-soluble, in which case permeability is increased. These authors established that: (1) large volumes of the drug-containing solution should be used to ensure exposure of the entire peritoneal surface; (2) to prevent systemic toxicity, the ratio of total body clearance to peritoneal clearance should be high; (3) because of limited penetration into tissue, the tumour to be treated should have small bulk; (4) co-administration of drugs which impair the hepatic or renal (systemic) clearance of the drug should be avoided.

Unwillingness to initiate protocol studies with intraperitoneal chemotherapy at different stages in the natural history of gastrointestinal cancer has occurred for several reasons. First, the delivery of drugs by the schedules usually employed with systemic agents results in multiple delivery-related complications. Tenckhoff catheters used over prolonged periods routinely fail to give uniform intra-abdominal drug delivery. There is a natural fibrotic reaction to the plastic catheter. Also, many of the agents have a sclerotic effect on peritoneum. These two factors, together with the adhesive effects of surgery, cause drug delivery to be completely inadequate. Furthermore, most oncologists have been unwilling to accept that resection site and peritoneal surface recurrences are major factors in the natural history of these diseases. This is, in large part, due to the lack of radiological techniques to demonstrate recurrent tumour at these sites. This must be contrasted with the large number of radiological studies that precisely identify cancer within liver and lungs. The only accurate studies establishing recurrence patterns of gastrointestinal cancer are those based on autopsy series or reoperative experiences. If local and regional recurrences are accepted as important surgical treatment failures, the best adjuvant to prevent these recurrences would be early postoperative intraperitoneal chemotherapy. The rationale for the use of intraperitoneal chemotherapy as an adjuvant in the immediate postoperative period is given in *Table 1*.

Table 1 *Rationale for the use of immediate postoperative intraperitoneal chemotherapy for gastrointestinal cancer*

1. The resection site and peritoneal surfaces are at high risk for recurrence. These surfaces are fully exposed to intraperitoneal chemotherapy in the immediate postoperative period
2. Pharmacological studies show a favourable therapeutic ratio for ablation of residual tumour microemboli on peritoneal surfaces
3. In the postoperative period, the surgical techniques for drug delivery are simple. They reliably give uniform drug delivery to peritoneal surfaces
4. For most drugs, intraperitoneal delivery does not compromise systemic exposure. Regional chemotherapy administration causes increased local effects without decreasing possible systemic disease control
5. The cost of therapy is minimal The patient is already in the hospital recovering from surgery. No expensive postoperative visits to receive other forms of adjuvant chemotherapy are required
6. There is minimal increased postoperative morbidity and no increased mortality with immediate postoperative intraperitoneal chemotherapy

The technique of immediate postoperative chemotherapy is quite simple. It involves inserting a Tenckhoff catheter at the completion of surgery to remove a primary gastrointestinal cancer. In the immediate postoperative period the catheter must be flushed with isotonic peritoneal dialysate fluid at a moderate rate. We use 1-litre abdominal lavage every hour for 4 h and then every 4 h until intraperitoneal chemotherapy begins. This fluid exchange ensures patency of the catheter by preventing fibrin and debris from collecting in it. A further advantage from this lavage of the peritoneal space may be the removal of growth factors. Inflammatory cells and healing tissue produce a variety of growth factors which may provide an environment in which residual carcinoma cells proliferate[130]. Colonic tumour cells have certainly been found to have enhanced growth rates in the presence of the typical inflammatory response preceding wound repair (unpublished results cited in Reference 131). We have shown that the intraperitoneal polymorphonuclear leucocytosis from inflammation in response to surgery subsides within 4 days[132].

On the first postoperative day, the intraperitoneal chemotherapy begins. One litre of dialysate containing chemotherapy is run through the Tenckhoff catheter in approximately 15 min. The catheter is then clamped until the next dose is due, at which point remaining fluid is allowed to run out. At all times, a strict aseptic technique is used when dealing with the catheter tip and with the skin exit site of the Tenckhoff catheter.

We have chosen to study the intraperitoneal pharmacology of a relatively small number of drugs (*Figure 2*). They all have certain characteristics that make them suitable for study, namely: (1) well documented use in systemic therapy; (2) a response rate greater than 20 per cent when used in gastrointestinal malignancy, (3) using Dedrick's criteria for intraperitoneal drug selection, all have potentially good characteristics and should provide a significant pharmacological advantage. Some of the drugs that we use, such as doxorubicin, may be questioned on grounds of chemical peritonitis[133] or toxicity. However, in animal studies, intraperitoneal doxorubicin has been shown to be very effective[133] and has the potential for intralymphatic activity when used with lipid microspheres[134].

The ideal regional chemotherapy regimen will not only treat residual intraperitoneal tumour, but will retain the possible systemic effects of these drugs. With intraperitoneal 5-FU administration, the plasma level of 5-FU 30 min after a 20 mg/kg dose approaches 30 per cent of that from a bolus dose of intravenous 5-FU of 15 mg/kg[135–137] and is 20 times that from a continuous infusion of 30 mg/kg per 24 h[138,139].

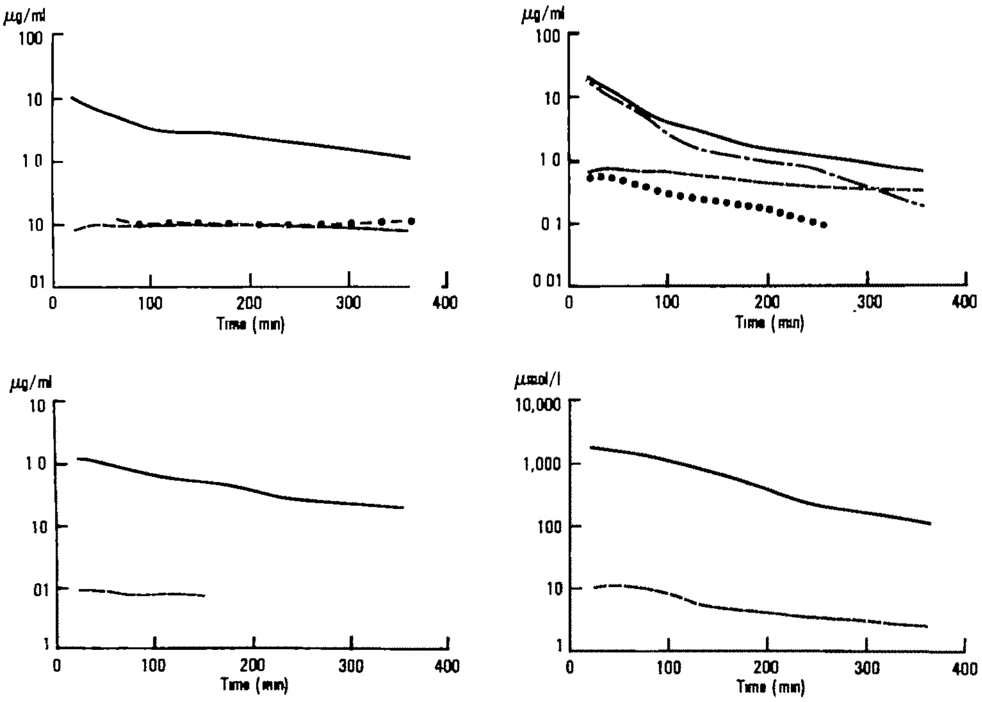

Figure 2 *Concentration* versus *time curves for four drugs effective in the treatment of gastrointestinal cancer and administered by the intraperitoneal route in the early postoperative period.* **a** *Concentrations in peritoneal fluid (——), portal plasma (●) and peripheral plasma (– – –) after intraperitoneal Mitomycin C (12 mg/m² in 2 litres).* **b** *Concentrations in peritoneal fluid (——), filtered peritoneal fluid (— - —), peripheral plasma (– – –) and filtered peripheral plasma (●) after intraperitoneal cisplatin (40 mg/m² in 2 litres).* **c** *Concentrations in peritoneal fluid (——) and peripheral plasma (– – –) after intraperitoneal doxorubicin (2 5 mg in 2 litres).* **d** *Concentrations in peritoneal fluid (——) and peripheral plasma (– – –) after intraperitoneal 5-fluorouracil (20 mg/kg in 2 litres)*

The area under the concentration *versus* time curve for the plasma level achieved from an intraperitoneal dose is considerably greater than that from an intravenous bolus but is associated with a lower likelihood of systemic complications.

Some agents have already been studied in detail in delayed postoperative intraperitoneal chemotherapy, notably 5-FU[140–1145], doxorubicin[146,133] and cisplatin[147]. A direct comparison of intraperitoneal *versus* intravenous 5-FU has been undertaken[148] and although no difference in survival was apparent, the natural history of colonic cancer was significantly altered by the intraperitoneal 5-FU, resulting in diminished peritoneal tumour implantation. The fact that no survival benefit was demonstrated following intraperitoneal chemotherapy may have been due to delay in chemotherapy administration and to the fact that patients with advanced cancer often have a combination of local–regional and distant disease.

Intraperitoneal penetration of tumour deposits by drugs is known to be limited; agents such as doxorubicin probably penetrate only a few cell layers[149,150] whereas cisplatin may penetrate as far as 2–3 mm[151,152]. Clearly a major rate-limiting factor in intraperitoneal chemotherapy will be this penetration and this may explain the varied success of studies so far using other agents such as methotrexate[153], melphalan[154], Mitomycin C[155] and 5-FU[148].

Systemic chemotherapy has been compared with intraperitoneal chemotherapy with respect to frequency of toxic reactions[148]. No difference in the incidence of toxicity was noted between the two groups but the severity of toxic reactions in the intraperitoneal group was markedly reduced. Toxicity from intraperitoneal therapy appears to be limited to local complications such as chemical peritonitis[146], escape of drug into subcutaneous tissues[156], and abdominal pain[141]. The reason for the reduced systemic toxicity is simply that if the appropriate drug is chosen, then the extraperitoneal systems will not be exposed to as high a level of drug as the intraperitoneal cavity. Thus, although local toxicity problems may occur as frequently with intraperitoneal 5-FU as systemic toxicity with intravenous 5-FU, the nature of the complications is less serious for the patient. This has been the case with early postoperative intraperitoneal chemotherapy in that there has been minimal myelosuppression.

Widespread intra-abdominal disease is not suitable for treatment with intraperitoneal chemotherapy. The exception to this rule is those patients with pseudomyxoma peritonei where the tumour cells are bathed in a large quantity of mucus. This makes an ideal medium for penetration by intraperitoneal chemotherapy and good results have been reported[157].

Pharmacokinetic studies are an essential part of early intraperitoneal chemotherapy studies. A typical study is demonstrated in *Figure 2*, which shows the concentration *versus* time curve for four drugs effective in the treatment of gastrointestinal cancer. The pharmacological advantages of intraperitoneal 5-FU chemotherapy used in the early postoperative period compare well with those reported by other authors where patients were not treated immediately after operation and therefore had a more normal peritoneal cavity[143]. Our intraperitoneal concentration *versus* time curve would appear to be slightly different: the possible reasons for this may be related to the presence of fibrin in the peritoneal cavity. In the immediate postoperative period there is a considerable sequestration of fibrin on the traumatized tissues. This fibrin may act as a mixing barrier which might alter the diffusion of small molecules.

The management of patients with gastrointestinal malignancy should be based on the knowledge that up to 40–50 per cent of patients will have intra-abdominal recurrence. New treatment plans should make use of the pharmacological advantage of intraperitoneal chemotherapy demonstrated so far. It is to be hoped that the alteration in natural history that has been achieved can be translated into improved survival. It will clearly be some time before the appropriate doses and regimens are determined, following which phase III studies would be required. The preliminary results of the therapy would appear to give reason for cautious optimism that the survival benefit for patients with gastrointestinal malignancy can be increased. We would suggest that early postoperative intraperitoneal chemotherapy could become part of a treatment strategy, which also makes use of preoperative radiotherapy and surgery as sequential multimodality adjuvant regional therapies to treat patients with gastrointestinal malignancy[143].

Survival differences in patients treated with early postoperative intraperitoneal chemotherapy cannot be seen to-date. The initial dose escalation studies were performed in 1987, so that limited follow-up is available. To-date, no randomized controlled studies have been initiated. However, clinical follow-up strongly suggests that the natural history of gastrointestinal cancer is modified by early postoperative intraperitoneal chemotherapy. Resection site recurrence and spread on peritoneal surfaces has not been seen in the follow-up of treated patients. Systemic disease recurrence has been documented with the expected recurrence rates.

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Paper accepted 2 May 1989

Examinations leading to the FRCS diploma

At the Annual Meeting of the Association of Surgeons of Great Britain and Ireland, with the President, Professor Sir Patrick Forrest in the Chair, it was unanimously agreed that the following statement represented the views of the Association:

The Association of Surgeons of Great Britain and Ireland accepts that the FRCS diploma is no longer a qualification which signifies sufficiency of knowledge in all areas of surgery. This position has arisen by the step-to-step development of a series of major specialties (e.g. orthopaedics, urology, etc.) within what used to be general surgery, each of which requires an extensive period of training following acquisition of the FRCS diploma as we now know it. These specialties do not accept that the present Fellowship is appropriate to their needs. They recognize the need for, and indeed demand, a stringent assessment of competence during the training period.

General surgery, as is now defined, i.e. gastrointestinal, breast and endocrine, vascular and transplant surgery, trauma, etc. is no different from any other surgical specialty, demanding similar periods of specialty training and assessment of knowledge. Logically this assessment can only be held during that period of specialist training, i.e. after the time of the present FRCS. The Association believes that it is at this stage that the FRCS diploma should be awarded, as we understand is also the view of other specialty associations.

Were this to be agreed, a period of basic training before training in a specialty (including general surgery) is necessary during which time the young surgeon is exposed to surgery in all its various forms. This allows him or her to experience different surgical specialties and to decide about the direction in which his or her career should go. At this stage the young surgeon must be examined in knowledge which is common to all forms of surgical practice. This test of basic core knowledge should be in depth in selected areas. Detailed knowledge of much of general surgery is acquired during the higher surgical training period and cannot be assessed during this basic training period.

The Association cannot see that such an assessment of this basic core knowledge should require two separate examinations. It should be possible within the structure of a single examination, which would form Part I of the FRCS (new type). It would clearly be important that the young surgeon received some formal affiliation to a College after passing this examination; but it is inappropriate that this should be the Fellowship.

Those currently enrolled in higher training programmes in general surgery require special consideration and should not be eligible to take any additional examinations.

The Association therefore wishes to state as its views that:

1. General surgery (i.e. surgery of the gastrointestinal tract, breast and endocrine, vascular and transplant surgery, trauma, etc.) must now take its place alongside orthopaedics, urology, etc. as a specialty in its own right which merits similar periods of training and methods of assessment

2. Two examinations only should be necessary to assess the competence of a general surgeon to practise: the first an assessment of core knowledge including basic sciences common to all surgical specialties including general surgery; the other a test of knowledge in general surgery as a specialty

3. Although some form of college affiliation will be necessary after satisfactory completion of the first assessment, the FRCS diploma proper should be awarded only after both parts have been satisfactorily completed

4. Those enrolled in higher training programmes in general surgery at the time of these changes should not be eligible to sit a further examination.

Barry Jackson
Honorary Secretary

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Endoscopic palliation of malignant biliary obstruction in a child

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The palliation of malignant biliary obstruction by the endoscopic insertion of an endoprosthesis is rapidly gaining acceptance as a safer alternative to surgical bypass[1]. Endoscopic palliation has been restricted almost entirely to elderly, unfit patients, but we report here the successful use of the technique in a 2-year-old boy.

Case report

A 2-year-old boy presented with anaemia, hypertension and a rapidly enlarging abdominal mass. Laparotomy revealed a large tumour apparently arising from the right kidney and extending retroperitoneally across the midline. Resection was not possible because of extensive accessory vasculature and the envelopment of the aorta and vena cava by tumour. Although biopsies were not diagnostic the tumour was thought to be a nephroblastoma and the appropriate chemotherapy was begun. Four days after the laparotomy the child suffered a large haemorrhage into the tumour. Although the bleeding was eventually controlled by embolization of the renal artery the child remained gravely ill. Ten days later his condition had improved sufficiently to allow a second laparotomy. The tumour was found to be much smaller and considerably less vascular and a right nephrectomy was performed. Although the majority of the mass was resected, residual tumour remained around the duodenum, common bile duct and inferior vena cava. Postoperative recovery was soon complicated by progressive jaundice and the child's condition deteriorated rapidly. The serum bilirubin and alkaline phosphatase levels rose to 282 μmol/l and 1362 units/l respectively, and ultrasonography revealed markedly dilated intrahepatic and extrahepatic bile ducts. To avoid a third laparotomy it was decided to try to relieve the biliary obstruction by the endoscopic insertion of an endoprosthesis.

Duodenoscopy was performed under general anaesthesia using an Olympus JF-1T 10® duodenoscope (Olympus Keymed, Southend, UK). The pancreatogram was normal but retrograde cholangiography showed extrinsic compression of the distal bile duct with proximal dilatation (*Figure 1a*). Under radiological control a Teflon® (E.I. du Pont de Nemours and Company, UK) coated guide-wire was negotiated across the stricture and a 5-cm, 8 Fr Leung-Cotton-type endoprosthesis was then railroaded into position (*Figure 1b* and *c*). A sphincterotomy was not performed and the procedure was uncomplicated except for a transient, asymptomatic rise in the serum amylase over the following 18 h. The jaundice resolved steadily and the child's general condition began to improve. Histology of the tumour removed at the second laparotomy showed it to be an undifferentiated intrarenal neuroblastoma rather than a nephroblastoma and the chemotherapy was changed to a more appropriate regimen. The boy left hospital 1 month after the insertion of the prosthesis and at discharge was free of jaundice and had virtually normal liver function tests. He has now been followed up for 4 months and has completed six courses of chemotherapy. He has made good progress, the jaundice has not recurred and the residual tumour has shown some signs of regression.

Discussion

The value of diagnostic endoscopic retrograde cholangiopancreatography (ERCP) in paediatric practice is now well established[2], but the therapeutic procedures derived from ERCP have been used infrequently. We believe that this is the first report of an endoscopically inserted endoprosthesis used to relieve biliary obstruction in a child.

We used virtually the same technique and equipment as employed in adults, the only differences being the use of general anaesthesia rather than intravenous sedation and the insertion of a shorter, smaller calibre prosthesis. The procedure was entirely straightforward; not only did it result in the complete resolution of the jaundice, but it avoided the necessity of a third laparotomy in a seriously ill child and led to no additional morbidity. Biliary obstruction due to an incurable malignancy

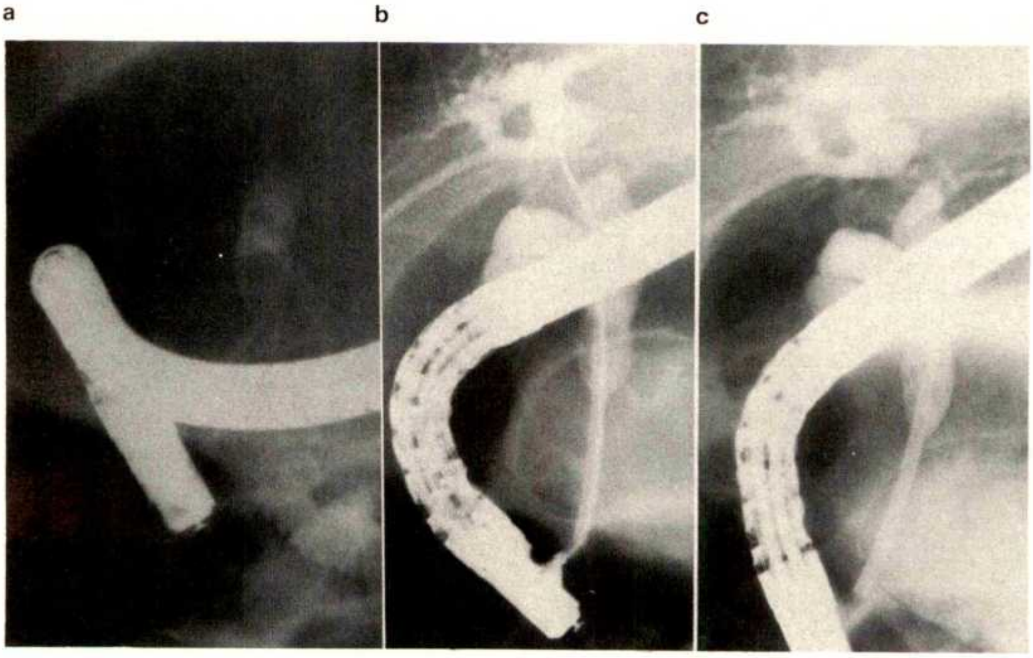

Figure 1 *Insertion of the endoprosthesis:* **a** *the extrinsic compression of the bile duct with proximal dilatation;* **b** *and* **c** *the endoprosthesis being railroaded into position. The filling defects in the bile duct are air bubbles not stones*

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is fortunately rare in children. However, when such an event occurs we suggest that the use of endoscopic palliation should be considered, and experienced endoscopists should not be reluctant to attempt the procedure in children.

Intrarenal neuroblastoma is a rare tumour and our case illustrates how it can be readily mistaken for the commoner Wilms' tumour. Rosenfield and colleagues have described six similar cases which were clinically and radiologically indistinguishable from Wilms' tumour[3]. It is unclear whether these tumours arise from intrarenal rests of neural crest tissue or originate in the adrenals and invade into the kidney. They are usually undifferentiated, aggressive tumours and have a poor prognosis.

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Surgical workshop

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New way to take pinch grafts

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Pinch grafts are traditionally harvested from an anaesthetized square or rectangle of skin, leaving intact skin between excised areas. This practice is time consuming and leaves a large raw area which is often more uncomfortable for the patient than the wound that is being treated.

We have modified the technique by excising a 3-mm wide strip of skin (*Figure 1*) which is then cut into 3-mm lengths. The strip of skin is incised obliquely so that the edges of the strip are partial thickness to mimic this valuable characteristic of pinch skin grafts. It is essential that the skin is carefully cleaned of any subcutaneous tissue before the strip is subdivided into its short lengths. The donor site is closed with a subcutaneous Prolene® (Ethicon Ltd., Edinburgh, UK) suture to give a linear scar which, if the site has been well chosen, is unobtrusive and almost painless.

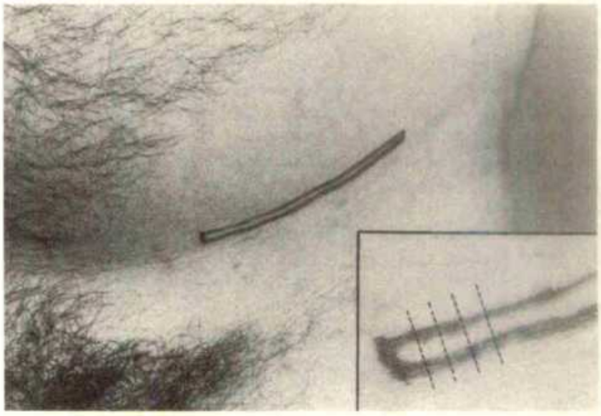

Figure 1 *Skin strip for pinch grafts. The 3-mm wide strip is cut into 3-mm lengths (inset)*

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British Association of Endocrine Surgeons

Abstracts of papers presented at the Ninth Meeting of the British Association of Endocrine Surgeons, Lille, France, 26 May 1989

Nucleolar organizer regions and cell ploidy in the interpretation of parathyroid histology

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The accurate histological differentiation between adenomas, hyperplastic and normal parathyroid glands is vital to the correct operative strategy in patients with primary hyperparathyroidism. However, this distinction may be unclear by conventional histological techniques.

Recent reports suggest that the number of nucleolar organizer regions (NOR) per nucleus may facilitate the distinction between malignant or benign or normal cells. This study comprised 27 paraffin-fixed sections of parathyroid tissue from patients who had undergone surgery for primary hyperparathyroidism. Eleven glands were considered on conventional histological criteria to be hyperplastic, ten adenomatous and six normal. The number of NOR per nucleus was counted in 50 cells per slide. DNA flow cytometry was also performed on 20 sections of parathyroid tissue using a Becton–Dickinson FAC scan (Becton-Dickenson UK Ltd., Oxford, UK) with on-line computer; 10 000 cells per section were counted and the results analysed with standard DNA cell-cycle software using a sum of broadened rectangles model. Seven glands were hyperplastic, six adenomatous, four normal and three were carcinomas.

The mean NOR count per nucleus in normal parathyroids was 3·1 (range 2·9–3·4) in contrast to adenomas (mean 4·1; range 3·7–4·4) and hyperplastic glands (mean 4·3; range 3·7–4·7). Normal glands had a lower NOR count than abnormal glands ($P<0\cdot05$, Mann–Whitney U test). DNA analysis showed 16 of 20 (80 per cent) parathyroid sections to be diploid; four glands (two adenomas, one hyperplastic and one carcinoma) were aneuploid.

We have subsequently performed NOR staining successfully on frozen sections of parathyroid tissue. The technique may have some potential value as an indicator at the time of surgery as to whether a parathyroid gland is normal or abnormal; in contrast, cell ploidy is unlikely to be useful.

Flow cytometric analysis of phaeochromocytomas and paragangliomas: prognostic significance of ploidy

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It is generally conceded that to distinguish histologically benign from malignant phaeochromocytomas (Ph) in the absence of demonstrated local invasion or metastatic disease is not reliable. Even though only approximately 10 per cent of Ph ultimately prove to be malignant, this figure rises to nearly 40 per cent in paragangliomas (Pa). An expedient method which would provide prognostic information would be valuable. We previously reported that patients whose Ph were DNA normal (diploid) by flow cytometric analysis followed a benign clinical course[1]. The purposes of this study were to enlarge the previous study group of Ph and to analyse Pa by the same technique.

The prognostic evaluation, operative procedure, histological assessment and follow-up clinical course were investigated. Tissue preparation of dissociated, stained nuclei and flow cytometric histograms were as described previously. Satisfactory histograms were achieved on paraffin-embedded tumours from 180 patients. The average age of patients was 44 years (range 3–82) with 100 men and 80 women.

Relating DNA histograms to clinical outcome, with a mean follow-up of 10·1 years (range 1 month–36·5 years), DNA histograms were classified as shown in the *Table*.

All patients with DNA normal Ph or Pa (mean follow-up >11 years) had no evidence of malignancy by either histology or subsequent clinical course. By contrast, tumours with either tetraploid/polyploid (T/P) or aneuploid (A) histograms exhibited malignant characteristics significantly more frequently than DNA normal tumours ($P<0\cdot05$).

	Evidence of malignancy*		
DNA histogram pattern	(−)	(+)	Total
Ph			
Nl	62 (100)	0 (0)	62
T/P	40 (74)	14 (26)	54
A	40 (75)	13 (25)	53
Total	142 (84)	27 (16)	169
Pa			
Nl	3 (100)	0 (0)	3
T/P	3 (75)	1 (25)	4
A	2 (33)	4 (67)	6
Total	8 (62)	5 (38)	13

*Tumour invasion, local recurrence, or distant metastases; Nl, normal (diploid); T/P, tetraploid/polyploid; A, aneuploid. Values in parentheses are percentages

These results confirm the value of flow cytometric DNA ploidy analysis in yielding useful prognostic information for patients with Ph and Pa.

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Influence of adenoma weight on the secretion of intact parathyroid hormone (PTH) in primary hyperparathyroidism

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A sensitive and specific immunochemiluminometric assay for intact (1–84) parathyroid hormone (PTH) has provided enhanced diagnostic accuracy in hyperparathyroidism and facilitated investigation of the mechanisms of PTH secretion[1].

The present study examines the relationship between preoperative serum PTH concentration and parathyroid adenoma weight in 44 patients undergoing surgery for primary hyperparathyroidism due to single gland disease. Mean(s.d.) preoperative corrected serum calcium was 2·86(0·23) mmol/l. Maximum serum PTH concentration ranged from 8·5 to 177·4 pmol/l (median 23·2 pmol/l). Adenoma weight ranged from 140 to 15 230 mg (median 760 mg). There was no significant correlation between preoperative serum calcium and either PTH concentration or adenoma weight ($r=0\cdot465$, $r=0\cdot381$ respectively). There was, however, a highly significant correlation between PTH concentration and adenoma weight ($r=0\cdot850$, $P<0\cdot0005$). Patients with adenomata heavier than 750 mg had a lower circulating PTH level per mg adenoma than those with smaller glands ($P<0\cdot00001$, Mann–Whitney U test).

PTH secretion by dispersed parathyroid adenoma cells was examined *in vitro*. The mean(s.d.) PTH secretion rate (pmol/10^5 cells/h) in low calcium medium (0·5 mM Ca^{2+}) from eight adenomata weighing <1000 mg was 91·2(143), there being no correlation between secretion rate and original gland weight. Two large adenomata weighing 2700 and 4200 mg secreted only 2 and 42 pmol/10^5 cells/h respectively.

We conclude that although *in vivo* there is a strong correlation between intact PTH secretion and adenoma weight, larger glands appear to secrete less PTH per unit weight and per unit cell *in vitro* under conditions of maximum stimulation.

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Hyperparathyroidism and pancreatitis

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The relationship between hyperparathyroidism (HPT) and pancreatitis is controversial, but HPT-induced hypercalcaemia is considered to be a rare cause of pancreatitis. A review of 650 consecutive parathyroidectomies revealed 15 cases of pancreatitis associated with HPT, an incidence of 2·3 per cent. In 14 cases acute pancreatitis was the presenting factor and in one case pancreatitis developed as a result of post-parathyroidectomy hypocalcaemia. All patients were hypercalcaemic, mean 3·0 mmol/l (2·6–4·2). The patient with hypocalcaemic pancreatitis had a calcium level of 1·79 mmol/l. Two cases had recurrent acute pancreatitis and one patient developed chronic pancreatitis. Four patients had pancreatic pseudocysts, two of which were drained surgically. One patient had a total pancreatectomy for chronic pancreatitis. There were no new episodes of pancreatitis after parathyroidectomy.

The parathyroid histology was adenoma in ten cases and nodular hyperplasia in five cases All patients became normocalcaemic post-parathyroidectomy except for one who remained hypercalcaemic.

In conclusion, pancreatitis is a complication of HPT. In patients ill with pancreatitis an early parathyroidectomy may benefit in recovery from pancreatitis.

Results of reoperation for persistent or recurrent secondary hyperparathyroidism

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Two hundred and fifty-eight patients were operated on for secondary hyperparathyroidism (HPT II) between 1971 and 1988 and 33 patients had 37 operations for persistent or recurrent HPT. There was no significant morbidity and no mortality.

Eighteen patients underwent 19 cervical reoperations, 12 of these patients having undergone initial surgery at another institution. The mean time to reoperation was 5·5 years. The surgical strategy in this group was to remove all parathyroid tissue in 16 patients with immediate transplantation in eight and delayed transplantation in two patients In two patients the hypertrophic remnant was reduced; 16 patients showed regression of hyperparathyroidism. Three patients died of causes unrelated to HTP II Currently, with a mean follow-up period of 3·5 years, 14 patients remain disease-free and one has persistent HPT.

Of 16 patients who underwent total parathyroidectomy with transplantation, 18 reoperations for graft reduction were required. The mean time to reoperation was 2·5 years. Hypertrophy of grafted fragments was observed in four patients Only two patients were cured by graft removal and residual parathyroid tissue after initial parathyroidectomy was suspected in five patients This was not confirmed in three (died) and two have not yet undergone reoperation. In the remaining nine patients the initial diagnosis eventually proved incorrect.

In conclusion, in considering reoperations for persistent or recurrent HPT II the correct diagnosis must be established. Reoperation after successful subtotal parathyroidectomy occurred infrequently (4·9 per cent) and was usually easily carried out with no morbidity. After total parathyroidectomy and transplantation recurrence can be due to graft-dependent disease or residual tissue within the neck or a combination of both

Total parathyroidectomy with autotransplantation for secondary hyperparathyroidism: a retrospective study

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Total parathyroidectomy with autotransplantation of an autologous parathyroid remnant to the forearm has now become a well established technique in the surgical management of secondary hyperparathyroidism. Between 1979 and 1986, 20 patients underwent this procedure at the Royal Infirmary of Edinburgh. Mean patient age at the time of surgery was 37·2 years with equal sex distribution and patients were followed up for a mean period of 52 months. All patients had long-standing chronic renal failure, having received renal replacement therapy for a mean of 9·8 years preoperatively and alphacalcidol for a mean of 3·3 years preoperatively. Surgery was performed for severe secondary hyperparathyroidism failing to respond to medical management with hypercalcaemia in 80 per cent, unacceptable symptoms in 65 per cent and soft tissue calcification in 45 per cent of patients. Sixteen patients had a good result from surgery with symptomatic relief, restoration of calcium homeostasis and evidence of bone healing The remaining four patients developed recurrent hyperparathyroidism with subsequent graft revision giving a good result in two and an unsatisfactory result in two There were no cases of permanent total hypoparathyroidism

Parathyroid function after surgery for Graves' disease assessed by a sensitive assay for intact (1–84) PTH

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Persistent hypocalcaemia (serum Ca <2 mmol/l and serum phosphate $>1{\cdot}3$ mmol/l, or serum Ca $<1{\cdot}9$ mmol/l) was recorded in four of 326 patients (1·2 per cent) who underwent bilateral thyroid surgery between January and August 1988

The fall in serum calcium following thyroidectomy for Graves' disease may reflect inadvertent removal or devascularization of parathyroid tissue, increased bone uptake of calcium, or a change in size of the intravascular compartment[1]. In contrast to previous studies we have used a sensitive and specific immunoradiometric assay for biologically active parathyroid hormone (PTH) to assess parathyroid function after surgery for primary autoimmune thyrotoxicosis

Venous blood samples after overnight fast were obtained from 11 patients (nine women and two men) immediately before and days 1–4 after thyroidectomy for Graves' disease. Serum was subsequently batch assayed to measure calcium, phosphate and PTH levels, thyroid status and renal function.

Symptomatic postoperative hypocalcaemia in two patients (group A) was associated with subnormal serum calcium and PTH levels throughout the period of study. In six asymptomatic patients (group B) the maximal postoperative incremental change in PTH ranged from -32 per cent to -67 per cent of the preoperative value; transient hypocalcaemia (serum Ca <2 mmol/l) was observed in five of these patients. In a further three asymptomatic patients (group C) the maximal postoperative incremental change in PTH ranged from $+17$ per cent to $+100$ per cent with transient hypocalcaemia recorded in two patients

In this study a low serum calcium in association with subnormal PTH values (group A) or an inappropriate fall in PTH (group B) would appear to suggest parathyroid insufficiency (usually subclinical) as the major cause of hypocalcaemia following thyroidectomy.

1 Percival RC, Hargreaves AW, Kanis JA The mechanism of hypocalcaemia following thyroidectomy *Acta Endocrinol* (*Copenh*) 1985; **109**: 220–6.

DNA aneuploidy in follicular neoplasms of the thyroid

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DNA aneuploidy is a feature of malignant disease and is a significant prognostic factor in differentiated thyroid carcinoma. Although described in some benign tumours and premalignant conditions, it has been suggested that DNA aneuploidy may be of value in distinguishing benign from malignant follicular thyroid neoplasms[1].

The nuclear DNA content of 64 follicular thyroid neoplasms (52 adenomas and 12 carcinomas) was determined by flow cytometric analysis of paraffin embedded material. technically satisfactory preparations were achieved in 57 cases. In 22 follicular adenomas DNA analysis was also performed on fresh material obtained by fine needle aspiration from the surgical specimen

An aneuploid DNA profile was obtained on analysis of fixed tissue in eight of 45 follicular adenomas (18 per cent) and three of 12 follicular carcinomas (25 per cent). DNA aneuploidy was observed in five of the 22 (23 per cent) fresh preparations from adenomas.

There were no distinguishing cytological features between follicular adenoma and carcinoma of the thyroid The only accepted criteria for the diagnosis of follicular carcinoma are the presence of vascular or capsular invasion which may be apparent only after meticulous histological examination. No difference was found in the DNA profiles of benign and malignant follicular neoplasms. Follicular neoplasia may be regarded as a single entity with a low incidence of local and distal spread

1 Greenbaum E, Koss LG, Elequin F *et al*. The diagnostic value of flow cytometric DNA measurement in follicular tumours of the thyroid gland. *Cancer* 1985, **56**: 2011–18

Long-term endocrine function of intraportal and intrasplenic islet autografts in cynomolgus macaques

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The extent to which isolated islet transplantation in diabetic recipients restores pancreatic endocrine function may be taken to be a measure of its success

After total pancreatectomy isolated cynomolgus islets were prepared by a technique developed for human islet isolation, then autografted. Graft endocrine function was assessed by measurement of plasma glucose, insulin and glucagon following intravenous administration of bolus and low-dose continuous infusions of glucose, alanine and arginine 6 weeks, 3 months, 1 year and 2 years after grafting

Within the first 3 months animals with intraportal autografts displayed fasting normoglycaemia but mildly impaired glucose handling, with qualitatively normal though quantitatively reduced insulin and glucagon responses. Hormonal responses to alanine and arginine were also qualitatively normal, though quantitatively reduced Animals with intrasplenic autografts had poorer graft function Long-term graft function correlated with insulin responses to glucose 6 weeks after grafting ($r_s = 0{\cdot}91$, $P < 0\ 001$), two animals with intraportal grafts which have maintained fasting normoglycaemia for over 3 years consistently displayed the most nearly normal endocrine responses

These results suggest that beta cell reserve is a determinant of islet graft survival and support the feasibility of isolated islet transplantation in selected patients with diabetes mellitus

Phaeochromocytoma precipitated by premedication

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A 67-year-old man with a 9-month history of hypertension presented for repair of an inguinal hernia. Examination was unremarkable with a maximum BP of 170/110 mmHg. Thirty minutes after intramuscular premedication with pethidine and atropine the patient felt 'unwell' and experienced retching and facial flushing. His BP was 150/90 mmHg and pulse 110 b.p.m. In the operating theatre his symptoms had receded and anaesthesia was induced. The anaesthetic included thiopentone, suxamethonium to facilitate intubation, nitrous oxide, isoflurane, droperidol, and a bupivacaine caudal. Within 15 minutes he became cyanosed, hypoxic, developed pulmonary oedema, followed later by paroxysms of hypertension (systolic BP 240 mmHg) and tachycardia (150 b.p m), with pulmonary artery occlusion pressure (PAOP) >40 mmHg in the presence of a normal CVP Urinary analysis confirmed the diagnosis of phaeochromocytoma (normetadrenaline 1100 μmol/24 h, metadrenaline 188 μmol/24 h, 3 methoxytyramine 5·8 μmol/24 h Alpha and beta blockade controlled BP, heart rate and PAOP and the pulmonary oedema and blood gases improved Eight days after the initial episode the patient developed a Gram-negative septicaemia from which he died. Post mortem confirmed a phaeochromocytoma in the right adrenal.

There are no other reports where premedication has precipitated an adverse reaction in undiagnosed phaeochromocytoma. Drugs that release histamine such as pethidine can precipitate a crisis[1], but other anaesthetic agents including droperidol[2], or surgery itself, may be triggers An idiosyncratic reaction to premedication should raise the possibility of an undiagnosed phaeochromocytoma.

1. Hull CJ. Phaeochromocytoma. *Br J Anaesth* 1986, **58** 1453–68
2 Montiel C, Artalejo AR, Bermejo PM, Sanchez-Garcia P. A dopaminergic receptor in adrenal medulla as a possible site of action for the droperidol-evoked hypertensive response. *Anesthesiology* 1986. **65**: 474–9.

Preoperative parathyroid localization by thallium isotope scintigraphy and ultrasonography: a comparative prospective study

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Preoperative identification of the location of a parathyroid adenoma should allow reduced operating time and morbidity and perhaps a unilateral neck exploration. A variety of preoperative localization procedures have been investigated (notably thallium isotope scintigraphy and ultrasonography) without clear comparison between the investigations or demonstration of benefit to either surgeon or patient

From November 1983 to January 1988 a prospective study of 71 consecutive patients coming to first neck exploration for primary hyperparathyroidism was conducted. Both localization procedures (thallium scintigraphy and ultrasonography) were employed in each patient and a comparison with the operative findings was undertaken. Data were analysed by a combination of Mann–Whitney *U* test, decision matrix analysis and Baye's theorem as described by McNeil[1]. Both investigations had a high specificity (91 5 per cent and 94 5 per cent for thallium scanning and ultrasonography respectively), but a low sensitivity (46 6 per cent and 21 4 per cent). Despite accuracy rates for all glands of 80 per cent and 75 per cent respectively, both scans proved consistently ineffective in localizing adenomas weighing less than 500 mg, over 80 per cent of which went undetected. The low sensitivity and failure to localize the adenomas most likely to present problems for the endocrine surgeon makes both of these localization procedures of limited value in the management of patients with primary hyperparathyroidism.

1 McNeil BJ, Adelstein SJ Determining the value of diagnostic and screening tests *J Nucl Med* 1976, 7 439–48.

Dyshormonogenetic goitres

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Eight patients, predominantly in the first two decades of life, with dyshormonogenetic goitre have been studied between 1986 and 1988. All patients were from a non-endemic goitre area and had raised serum thyroid stimulating hormone, an elevated radioactive iodine uptake and low serum T_3 and T_4 The diagnosis was confirmed by fine needle aspiration cytology Antithyroid antibody, both antimicrosomal and antithyroglobulin, helped to rule out thyroiditis. All except three patients were managed conservatively Surgery involved a near total thyroidectomy for cosmetic and pressure effects and one patient had a malignant lesion demonstrated by capsular infiltration and vascular invasion.

The need to identify the condition and refrain from surgery is stressed as partial thyroidectomy is inappropriate therapy

Thallium-201/technetium-99m subtraction scanning in persistent or recurrent hypercalcaemia following parathyroidectomy

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In a consecutive series of 728 patients undergoing thallium-201/technetium-99m parathyroid subtraction scans there were 19 patients with recurrent or persistent hypercalcaemia following previous parathyroidectomy.

The scans showed a hot spot in 12 patients and nine of these underwent repeat neck exploration. In eight of these patients an abnormality was found (seven adenomas, one recurrent parathyroid carcinoma) One patient whose scan was positive had no detectable parathyroid abnormality. The three patients with positive scans who did not undergo further surgery became normocalcaemic without treatment and the diagnosis remained uncertain.

In seven patients the scan was negative. Three of these patients did not undergo further neck exploration and subsequently became normocalcaemic. Four patients underwent further surgery despite a negative scan. In none was an abnormal parathyroid gland found in the neck.

Thallium-201/technetium-99m subtraction scanning thus detected all eight persistent or recurrently abnormal parathyroid glands in the neck (sensitivity, 1·0), although one definite and three possible false positive results were recorded. Specificity was 0·67 with no false negative results. There were no complications of the investigation.

It was concluded that thallium-201/technetium-99m subtraction scanning is helpful in the management of hypercalcaemia following previous parathyroidectomy.

'Scan-directed' unilateral neck exploration for parathyroid adenoma: a legitimate approach?

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In 75–85 per cent of patients with primary hyperparathyroidism (HPT) the underlying pathology is a solitary parathyroid adenoma. If preoperative localization studies can successfully identify the site of the adenoma, then routine exploration of the contralateral side of the neck would seem unnecessary in this large subgroup of patients.

Since 1983 we have used thallium-technetium isotope subtraction scanning for preoperative localization in all patients being submitted to operation for HPT, and since January 1985 we have adopted a policy of 'scan-directed' unilateral neck exploration for patients with a positive scintiscan and in whom an adenoma is found at the site suggested by the scan. All other patients have continued to have standard bilateral cervical exploration.

During the period 1985–88 a total of 90 individuals (74 women, 16 men) underwent 'first-time' neck exploration for HPT. In all 48 patients who had 'scan-directed' unilateral neck exploration a solitary adenoma was retrieved with return of the serum calcium to normal. Of 42 patients who had bilateral exploration 33 had a solitary adenoma, three had multigland hyperplasia and in six no abnormal parathyroid tissue was identified.

Mean operating time for the 48 patients who underwent unilateral neck exploration was 74 min; that for the group of 26 patients who had bilateral exploration for solitary adenoma following a negative or false positive scan was 95 min.

At a mean follow-up of 17·6 months (range 1–46 months) no patient who had undergone 'scan-directed' unilateral neck exploration for solitary parathyroid adenoma demonstrated persistent or recurrent hypercalcaemia.

Tc-99m RP30: a new agent for parathyroid imaging

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Thallium-201/Tc-99m pertechnetate subtraction scanning is the standard radionuclide method for localizing abnormal parathyroid glands. Tc-99m RP30 has been introduced as an alternative to Tl-201 in studying myocardial perfusion. Its use as an agent for parathyroid localization is described.

Eight patients with hyperparathyroidism have been studied with both the thallium-pertechnetate subtraction technique and also with Tc-99m RP30, and five of these have now undergone surgery. Three had solitary parathyroid adenomas which were correctly localized by both techniques; in two of these the adenomas were more readily demonstrated with Tc-99m RP30. One patient with renal hyperparathyroidism showed a similar pattern with both techniques, two of three abnormal parathyroid glands being localized and a 'false' positive thyroid adenoma. The fifth patient with metastatic parathyroid carcinoma was scanned and recurrent tumour demonstrated in the neck. This was accurately identified and at operation was easily located and removed.

These preliminary results indicate that Tc-99m RP30 may be a suitable technetium labelled alternative to Tl-201 for parathyroid localization, and is superior in some cases. Further studies are being undertaken to identify its role in parathyroid imaging.

Selective postoperative radio-iodine treatment of thyroid carcinoma

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In a consecutive series of 243 patients with differentiated thyroid carcinoma of follicular cell origin (Hürthle cell tumours excluded) a diagnostic imaging dose of 10 mCi ^{131}I (RAI) was administered 6 months after thyroidectomy and 4 weeks after cessation of thyroid hormone, *only* if cervical node or other evidence of metastases was present.

Patients with RAI uptake of $\geqslant$3 per cent (Group I) were treated with 150–200 mCi RAI. The total body scan was repeated 6 months later to ascertain the absence of further uptake. Patients with $<$3 per cent uptake (Group II) were treated only with thyroid hormone, as were patients with no evidence of metastases (Group III). All patients were initially treated with total thyroidectomy, and modified neck dissection if cervical lymph node metastases were present.

There were 20 patients in Group I (8·2 per cent), 62 in Group II (25·5 per cent) and 161 in Group III (66·3 per cent). The mean follow-up was 8·9 years in Group I, 8·4 years in Group II and 7·2 years in Group III. The median follow-up was 7 years for Groups I and II and 6 years for Group III. The age, sex and papillary/follicular distribution in all three groups was similar. During follow-up three patients (15 per cent) in Group I developed recurrent tumour, one patient (1·6 per cent) in Group II and none in Group III. Death rate from thyroid carcinoma was 5 per cent in Group I (one patient) and zero in Groups II and III.

In conclusion, the absence of cervical lymph node metastases or evidence of distant metastases in patients with differentiated thyroid carcinomas of follicular cell origin (Hürthle cell tumours excluded) seems to be a valid indicator that the disease is in its early stages and that in such patients (66 per cent in the present series) RAI studies and treatment are not necessary.

FNA cytology: responsibility for its diagnostic failure

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FNA cytology, when applied to thyroid lesions, is incapable of establishing a correct diagnosis in about 30 per cent of cases. In this prospective clinicopathological study an attempt was made to determine whether the technique of FNA or the current cytological knowledge was responsible for the recorded diagnostic failure.

On 23 randomly selected consecutive patients out of 140 who were operated on for thyroid lesions during a 1-year period (1986–1987), a peroperative FNA cytology (perop-FNA, direct vision of the lesion) was performed in 21 as well as a preoperative one (preop-FNA, indirect technique). In 17/23 of the same cases a smear of the cut surface of the lesion was also taken after a preoperative FNA cytology had been performed. The findings of the histological examination (final correct diagnosis) were compared with those obtained through the preop-FNA, the perop-FNA and the smear examination using the χ^2 test. Clinical information regarding the thyroid lesion was provided to the cytologist when examining the preop-FNA slide but not when studying the perop-FNA or the smear slide.

It was found that although the diagnostic accuracy of all the techniques studied was still the same when compared with the histological examination (70 per cent) ($\chi^2=16{\cdot}525$, $P=0{\cdot}257\times10^{-3}$), there was no statistically significant difference ($\chi^2=10{\cdot}4$, $P>0{\cdot}1$) when the comparison was made between the three studied techniques in all possible combinations.

It is assumed that in this series of thyroid lesions the technique of preop-FNA is not responsible (in comparison with cytology evaluation) for the previously recorded relatively high percentage of diagnostic failure.

Prospective study of thyroxine therapy in the management of benign solitary thyroid nodules

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With the use of fine needle aspiration biopsy (FNA), thyroid nodules that are proven benign are often followd up without surgical intervention. It is controversial whether thyroxine therapy is effective in suppressing the growth of these nodules

We studied 62 patients with solid benign colloid nodules proven by aspiration cytology, prospectively randomized into receiving thyroxine therapy or no therapy. There were 56 women and five men. Their mean age was 39 years The mean nodule size was 3·6 cm and mean duration of occurrence was 1 year. Serum thyroxine and thyrotropin in all patients were normal Thyrotropin releasing hormone tests performed on all patients were positive indicating thyrotropin responsiveness to suppression. The patients were reviewed at 6 months, 1 year, 1·5, 2 and 3 years.

In a group of 31 patients with no thyroxine therapy, nodules decreased in size in four, remained unchanged in 15 and disappeared in two patients Six nodules increased in size with no change in pathology on repeat FNA. Three became cystic and disappeared after aspiration. One carcinoma was detected at operation for rapid increase in nodule size.

In the group of 31 patients receiving thyroxine therapy, nodules decreased in size in seven, remained unchanged in 16 and disappeared in one patient Three patients had increased nodule size Three patients developed cystic changes and nodules disappeared after aspiration. One patient had repeat aspiration biopsy showing carcinoma and underwent surgery.

Our data show that about one-third of the patients had reduction in nodule size on follow-up and that thyroxine therapy does not appear to alter the natural course of benign colloid nodules.

Decision-making for modified neck dissection in the surgery of thyroid carcinomas: cost effectiveness of routine sampling of supraclavicular nodes with frozen sections

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Modified neck dissection (MND) is not carried out in surgery for thyroid carcinoma in the absence of grossly involved nodes, except for medullary thyroid carcinoma. Clinical node recurrence is uncommon at follow-up (5·7 per cent). Several authors report metastatic cancer in non-palpable nodes – up to 70 per cent on MND specimens The fear of overlooking occult metastatic deposits prompted us to sample all supraclavicular nodes and to rely on frozen sections (FS) to make a decision whether or not a MND should be carried out.

Of 289 consecutive patients operated on for thyroid carcinoma, 116 were submitted to supraclavicular node sampling with FS In 173 cases sampling was not done (palliative surgery, eight, lack of intraoperative diagnosis of carcinoma, 73) or for other reasons (absence of obvious nodes, 70, unavailable pathologist, 15, miscellaneous, seven). All specimens were reviewed by paraffin sections (PS)

Among the 116 patients, 23 had gross metastatic node involvement confirmed by FS^+ and PS^+, one had grossly equivocal node with FS^- and PS^+, and 92 had grossly normal nodes. In 89/92 (96·7 per cent) this was confirmed by FS^- and PS^-. In three (3·3 per cent) FS was positive, leading to MND, and PS confirmed metastatic involvement in two.

Thus, no more than 3 3 per cent of the grossly normal supraclavicular nodes contain metastases at the time of surgery. Routine node sampling with FS is not cost effective in decision-making for MND The surgeon may rely on clinical evidence of node involvement.

Annual Meeting of the British Association of Endocrine Surgeons

The Annual Meeting of the British Association of Endocrine Surgeons will be held in London in May 1990. Further details may be obtained from Mr A. Goode, Reader in Surgery at the London Hospital.

Correspondence

Size of T tubes and the radiologist

Sir

Interesting though the paper on T tube modification by Crnojevic *et al.* (*Br J Surg* 1989, **76**: 342–3) is, it is not clear from the results why the authors feel that smaller T tubes are preferable. The data clearly show that the force necessary to remove a sculpted T tube is equally low for all tube sizes between 12 and 18 French, the implication of this being that the risk of bile peritonitis is similarly low. One of the functions of the T tube is to allow access to the bile ducts for the non-operative management of retained stones. Percutaneous T tube track removal of stones[1] is simple, successful and safe but requires a T tube track of 14 French or larger. The alternatives of endoscopic removal[2] or surgery are more risky. As Crnojevic *et al.* indicate, the risk of bile peritonitis following T tube extraction is less than 1 per cent, but the risk of retained stones, even in the most experienced hands, is about 5 per cent[3]. Is it sensible on the basis of *in vitro* evidence to suggest that we should deprive ourselves of an effective method of treating a relatively common complication of bile duct surgery in order to avoid a rare complication? A compromise is necessary. Surely surgeons should use a 14 French sculpted T tube brought out subcostally in the right flank. This avoids the risks which may be associated with excessive force for the removal of the tube but allows T tube track extraction of retained stones.

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Partial cholecystectomy

Sir

The article by Winkler *et al.* (*Br J Surg* 1989; **76**: 693–5) continues the endless debate on cholecystostomy. We were surprised, however, that the authors, in their discussion, omitted to mention the third option, namely, partial or subtotal cholecystectomy. This procedure was described many years ago by Torek[1] and is well described in classical operative texts[2]. Recently, Bornman *et al.*[3] described its use in 18 patients with a 'difficult' gallbladder in portal hypertension and cholecystitis. During the last 3 years we have used this technique in 14 high risk patients (APACHE II>10) who underwent emergency operation for acute cholecystitis. Three patients suffered from a bleeding tendency (portal hypertension, overdose of warfarin, chronic haemodialysis). When performing this procedure we leave a 1 cm rim of the Hartmann's pouch tissue and buttress it over the opening of the cystic duct. The exposed and often necrotic mucosa of the posterior wall is vigorously destroyed with diathermy, an omental plug is brought into the site and a suction drain is left for 24–48 h.

One patient, on chronic haemodialysis and critically ill with acalculous cholecystitis died. The others recovered without complications.

Subtotal cholecystectomy is an attractive alternative to cholecystostomy or cholecystectomy in the high risk patients with a 'difficult' gallbladder. It avoids the potential complications of cholecystostomy (fortunately not encountered by Winkler *et al.*) and achieves the objectives of cholecystectomy. It is more suitable than cholecystostomy when the gallbladder is partially or totally necrotic. Subsequent interval cholecystectomy is not required. Like cholecystostomy it is a rapid and safe procedure.

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Colorectal cancer and cholecystectomy

Sir

I was disappointed to read the conclusions of the review on cholecystectomy and colorectal cancer The majority of papers in the literature have failed to find any association between colorectal cancer and cholecystectomy and of the 10 papers quoted by Moorehead and McKelvey as showing a positive correlation only 5 demonstrated an increased risk for all sites in the colon. The remainder observed an increase in certain sub-groups, e.g. females with rectal cancer[1] and such findings may be due to chance as analysing numerous subgroups for an association increases the possibility of finding a 'significant' association in one subgroup.

In the 5 papers where the whole colon was found to be at an increased risk of cancer after cholecystectomy the observed risk increases were of a moderate degree, mostly below two-fold and never exceeding three-fold and the relative risk was often not quoted or did not differ from unity.

The only prospective study[2] failed to find any increased risk in 16 773 patients undergoing cholecystectomy. The largest retrospective study[3] from California examined 5898 cases of colorectal cancer and 27 687 controls and also failed to find any increased risk of colorectal cancer after cholecystectomy yet this is not even quoted by the reviewers Moorehead and McKelvey's article is a highly selected review of the literature and many other negative studies, for example Reference 4, are not quoted.

The importance of any relationship between cholecystectomy and subsequent colon cancer is debatable. The increased risk, if real, is unlikely to be sufficient to justify the costs of screening in view of the huge number of patients who undergo cholecystectomy and would require follow-up.

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Gastric cancer: a 25-year review

Sir

In their review of the incidence and management of gastric cancer in the West Midlands, Allum *et al* (*Br J Surg* 1989; **76**: 535–40) point out that 80 per cent of patients presenting with disease are considered too extensive for radical surgery, while only 0·7 per cent had Stage I disease at presentation. Higher rates of detection for early lesions reported in other studies have been attributed to widespread use of upper gastrointestinal endoscopy. Allum *et al.* recommend a change in referral patterns, with early endoscopic assessment being encouraged for patients 'with any symptoms referable to the upper gastrointestinal tract' because it is not possible to be more specific about symptoms which may be correlated with the presence or extent of malignancy.

Implementation of these recommendations would have profound consequences on the use of resources. Dyspeptic symptoms are extremely common in the community[1] and may account for 3–4 per cent of patients seen in general practitioners' surgeries[2] Because only a minority of these patients will turn out to have serious disease on investigation, the majority, quite appropriately, are treated in general practice without the need for referral or investigation. If each general practitioner working in the catchment area of a typical district general hospital were to refer a single dyspeptic patient each week for endoscopy, this would result in an unsustainable workload of over 10 000 endoscopy requests each year. Clearer guidelines are required for the selection of patients requiring investigation.

Patients' age seems to be of particular importance. A number of studies have suggested that patients under the age of 45 years do not require investigation because gastric cancer is unlikely to occur in this age group. For example, in a consecutive series of 1386 patients with dyspepsia investigated by endoscopy and radiology during 1986, Williams *et al.*[3] found no cases of oesophageal or gastric cancer in those under the age of 45. Heatley and Rathbone[4] have also recently questioned the wisdom of enthusiastic investigations in an attempt to diagnose every case of early gastric cancer. Indeed, many of the recommendations about the use of H_2-receptor antagonists have been developed because of anxieties about 'missing' cancer by masking symptoms of ulcerating lesions and creating diagnostic delay. The suggestion that these agents should not be used before an endoscopic or radiological diagnosis is obtained would also lead to overwhelming numbers of hospital referrals. Investigation is, of course, required when symptoms fail to respond or recur after a course of treatment, with increasing age being a guide to the urgency of investigation.

In the absence of diagnostic symptoms or symptom complexes, the identification of early gastric cancer remains a challenge, but one which is unlikely to be met adequately by indiscriminate investigation of all patients with dyspeptic symptoms.

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Perforated peptic ulcer

Sir

We read with interest the article 'Operative mortality after perforated peptic ulcer' by Messrs Ball, Thomas and Evans (*Br J Surg* 1989; **76**: 521–2). The authors identified a group of elderly patients for whom surgery carries a high risk of mortality and suggested that the role of conservative treatment should be evaluated in this group of patients.

We recently conducted a randomized controlled trial comparing expectant treatment with immediate surgery in patients with perforated peptic ulcers[1]. Over a 13-month period 83 patients were randomized, 40 to conservative treatment and 43 to immediate surgery. The patients in the conservative group were re-examined by a senior member of staff at 12-hourly intervals and were operated on if there was no improvement. Of the 40 patients in this group, 11 (28 per cent) required operation. The mortality rate (5 per cent in each group) and morbidity were similar in the two treatment groups. The patient's age was an important determinant of successful conservative treatment; all eight patients under 40 years of age and 18 out of 23 aged between 40 and 70 sealed their perforation spontaneously, whereas only three out of nine patients over 70 years of age had spontaneous sealing ($P < 0.05$).

Elderly patients with perforated peptic ulcers are less likely to respond to non-operative treatment. These patients withstand continued intra-abdominal sepsis poorly. Although the risk of surgery is high, urgent laparotomy after adequate resuscitation offers the best chance of a successful outcome.

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Changing concepts in renovascular surgery

Letter 1

Sir

We read with interest the Leading Article by Bergentz and colleagues (*Br J Surg* 1989; **76**: 429–30). A further evolving concept which deserves mention, but which few authors have focused upon, is the approach one should adopt to renovascular problems in the presence of an abdominal aortic aneurysm.

We recently reviewed our series of 142 elective aortic aneurysms over a 40-month period and noted that 19 patients (13·4 per cent) required combined aneurysm surgery with renal artery reconstruction. Eight of these patients underwent surgery for the presence of one or more renal arteries arising from the aneurysm. Of the remaining 11 patients, nine (47·4 per cent of the 19 patients) required surgery for renal insufficiency, while in two cases the indication was clinically significant uncontrollable hypertension. Like our colleagues, we also had disappointing results with percutaneous transluminal angioplasty, particularly with ostium lesions.

Nine of the 19 patients underwent bilateral renal artery surgery, resulting in a total of 28 vessels being operated upon in the series. Main renal revascularization procedures included trans-aortic renal artery endarterectomy (TEA) alone in ten arteries or in combination with renal artery reimplantation in three arteries, renal artery reimplantation alone in eight arteries, and renal artery bypass grafting in four arteries utilizing a 5-mm thin-walled ePTFE graft.

We had one death postoperatively in the series owing to a disseminated intravascular coagulation. One patient developed a hemiparesis while a second patient suffered a myocardial infarction and a third patient suffered a pulmonary embolus. Both of the latter patients made a good recovery. Four patients suffered a temporary deterioration in renal function but had returned to their preoperative creatinine levels at 2-month follow-up. Long-term follow-up (mean 17 months) revealed that nine of 13 patients noted to be hypertensive on preoperative evaluation were cured or improved after surgery according to the criteria proposed by Dean *et al.*[1]. This included the two patients whose indication for operation was hypertension. In three patients hypertension was unchanged postoperatively, while it worsened in one patient requiring increased medication. Normal renal function was maintained in the 10 patients who had normal preoperative serum creatinine levels. No patient undergoing the combined procedure required permanent haemodialysis.

While our series is small, we feel that with careful preoperative assessment and appropriate surgical technique, combined abdominal aortic aneurysm resection and renal revascularization can be performed with a low complication rate. Until such time as the results of the prospective trial by Bergentz and colleagues comparing reconstructive surgery and percutaneous transluminal angioplasty are available, patients should not be denied this combined procedure, particularly where preservation of renal function is a primary concern.

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1. Dean RH, Keyser JE, Duopont DW, Nadeau JH, Meacham PW. Aortic and renal vascular disease—factors affecting the value of combined procedures. *Ann Surg* 1984; **3**: 336–44.

Letter 2

Sir

We read with interest the recent review article on renovascular surgery by Bergentz and colleagues (*Br J Surg* 1989, **76**: 429–30). We support their reccommendations for aggressive surgical management of acute renal artery thrombosis even in elderly patients.

An 80-year-old lady, who had been well apart from myocardial infarction 11 years previously, was referred by her family practitioner because of deteriorating renal function in association with hypertension. The blood pressure was poorly responsive to a combination of enalapril 2·5 mg and frusemide 40 mg (with potassium supplementation). Examination revealed a blood pressure of 180/90 mmHg supine and 170/90 mmHg upright. There was an ejection systolic murmur and an epigastric and femoral bruit, but pedal pulses were palpable. Investigations showed a urea concentration of 27·3 mmol/l, creatinine concentration of 446 μmol/l and potassium concentration of 5·7 mmol/l. Isotope estimation of glomerular filtration rate was 16 ml/min and demonstrated a non-functioning left kidney.

When the patient was telephoned to discontinue her potassium supplementation, she informed us that she had passed no urine for 20 h. She was seen urgently in the emergency department. She was in pulmonary oedema, but complained of no loin pain. Urea concentration was 31·6 mmol/l, creatinine concentration 599 μmol/l and potassium concentration 6·2 mmol/l. Ultrasound scan demonstrated an atrophic (6 cm) left kidney and a 9·5 cm right kidney. Following acute haemodialysis, an aortogram demonstrated occlusion of the left renal artery at its origin and of the right renal artery 2 cm from the origin. A gastroduodenal–renal artery end-to-end anastomosis was performed and she began to diurese during the surgical procedure. She required no further dialysis or hypotensive medications. At the time of discharge her creatinine concentration was 240 μmol/l.

We would like to draw attention to the role of gastroduodenal–renal artery bypass. In the elderly and hypertensive population, the aorta may be severely diseased and not easily amenable to renal artery bypass. Using gastroduodenal – (or hepatorenal) bypass will spare the patient the morbidity associated with aortic surgery.

In the setting of hypertension and moderate renal insufficiency, the onset of complete anuria should raise the suspicion of acute renal artery occlusion (either bilaterally, or to a solitary functioning kidney). Timely surgical intervention may obviate the need for long term renal replacement therapy in these patients.

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Extending surgical audit

Sir

Mr Macintyre is right to stress the importance of extending surgical audit to include data relating to the important aspects of outcome[1]. At present, most audits concentrate upon easily collected in-patient data rather than more complex issues such as survival, disease recurrence and quality of life indicators, information which may be of far greater importance to the patient. A major concern with the recent government proposals[2] is that, in the absence of data about the eventual outcome, there will be too much emphasis placed on data relating to resource management or short term indicators. It is not inconceivable that some of these measures are inversely related to long term outcomes To make decisions about referral or resource allocation based upon an audit which omits such indicators is an incentive to select more simple and cheaper treatments, possibly to the detriment of long term results

Full audit of follow-up data from out-patient clinics or postal questionnaires must be the ultimate aim, but it will take many years to implement, and many more before useful results emerge. In the mean time in-patient audit provides invaluable information for surgeons and managers. But can audit really be used as 'proven results' to guide patient and GP in the choice of referral hospital, firm or consultant? This would appear to raise a number of difficulties Results of audit are usually classified by diagnosis or operation and these may not be predictable at the time of initial referral. Information about outcome would have to be linked to data about patient mix and selection to prevent bias against those treating poor risk patients. Even if appropriate and accurate data could be delivered to the decision maker there would be few operations that are performed frequently enough for meaningful confidence limits to be placed on the incidence of complications or recurrence. If two surgeons have observed mortality rates of 5 and 10 per cent for the same operation they would have to do about 200 cases each before the difference would be significant. To demonstrate that poor results from one of a large number of units is anything other than a chance finding requires complex calculations on a large quantity of simplified data[3]

Audit may improve surgical practice but it seems unlikely that it will be able to furnish much in the way of hard statistical evidence as to the relative merits of different units. Medical students today are taught the importance of properly controlled and randomized trials Are we to see these principles eroded in favour of referral to the surgeon with the best result over the last 20 cases, or will general practitioners begin multi-centre, controlled trials with randomized referrals to different hospitals? Until better information is available it would seem preferable for referral patterns to continue to be governed primarily by 'personality and geographical proximity', rather than by inappropriate data, financial incentives and advertising

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Paralytic ileus: response to naloxone

Sir

Therapeutic use of opiates may be accompanied by adverse effects on smooth muscle function. For example, acute urinary retention may be precipitated by parenteral opiates[1] or sublingual buprenorphine[2]. Competitive receptor blockade with naloxone[3] will reverse many of these provoked retentions without loss of analgesia. Involvement of μ opiate receptors in other nerve plexes is less well documented. Opiates have been reported to cause paralytic ileus, but this association is rarely considered and therefore the effect of naloxone is unknown. We report the case of a 51-year-old man with a small cell carcinoma of unknown primary origin. The patient commenced on oral morphine sulphate tablets (MST) 30 mg tds 1 week before he was readmitted acutely with a 5-day history of absolute constipation On examination, he was found to have diffuse abdominal tenderness associated with ascites and a paralytic ileus As the MST might have contributed to his condition, 0·8 mg naloxone was administered intravenously. Bowel sounds returned dramatically within 1 min and he defaecated massively on three occasions within the next 10 min. This was accompanied by total relief of his diffuse abdominal pain.

Paralytic ileus is a frequent complication of many operations and its aetiology is often multifactorial. However, both exogenous and endogenous opiates may be implicated in its genesis As reversal is rapid, this report may suggest an acceptable alternative therapy for selected patients with paralytic ileus.

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Pleomorphic adenomas of the parotid salivary gland

Sir

I read Mr H. Lawson's article on capsular penetration and perforation in pleomorphic adenomas of the parotid salivary gland with great interest (*Br J Surg* 1989, **76**: 594–6). He kindly refers in his introduction to my recent article[1]

Unfortunately, I am misquoted. The figure of 1·6 per cent refers to rate of accidental rupture of the tumour (one of 64 cases), and not to recurrence rate. There were no recurrences and are still none, in a series which has grown to 74 new pleomorphic adenomas with a median follow-up of 5 years.

I am quoted as advocating removal of the tumour with only a covering of normal parotid This confusing statement is presumably a typographical error. It would be correct to say that I advocate a small covering of normal parotid wherever possible.

My concern about Mr Lawson's study is that he refocuses attention on the observation of capsular penetration reported by Patey and Thackeray in 1957. This oft-quoted observation seems to have blinded most surgeons from accepting the obvious, this being that, with rare exceptions, recurrence of a pleomorphic adenoma is due to a macroscopic accidental rupture of the capsule, basically a technical error. Once this is more widely recognized, the observation of microscopic penetration of the capsule will be seen as an interesting but largely irrelevant observation and the controversy of formal superficial parotidectomy against enucleation will cease

The precise method of removal is unimportant provided that the capsule is not ruptured. In practice this is best achieved by early exposure of the facial nerve and removal of the tumour with a modest covering of parotid In deep tumours and those in contact with the nerve, this will not be possible, while in very superficial or peripheral tumours a careful local dissection may well be the procedure of choice.

Whatever the situation, a very low recurrence rate can be anticipated provided the tumour is removed intact.

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Sister Mary Joseph's nodule

Sir

The article by Heatley and Toner (*Br J Surg* 1989; **76**: 728–9) in the July issue of the journal states that metastasis to the umbilical skin was first described by Storer, and is often known as Sister Mary Joseph's nodule I would like to point out that Walshe[1] in 1846 reported that Tanchov in reviewing the data from the Mortuary Registers of Paris and two adjacent *arrondissements* found 9118 deaths from cancer from 1830 to 1840 inclusive, and found that the umbilicus was involved in two cases.

Lage[2] in 1847 reported a case of colon cancer with umbilical metastasis. Storer[3] in 1864 reported on a lady who at autopsy was found to have carcinomatosis from carcinoma of the stomach with umbilical metastasis.

Sister Mary Joseph[4] (1856–1939) was superintendent of St. Mary's Hospital when she drew the attention of Dr William Mayo to this sign of intra-abdominal malignancy. The eponym, Sister Mary Joseph's nodule, was first described by Hamilton Bailey in the 11th edition of his book on physical signs in clinical surgery in 1949, and has since been used by generations of physicians.

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1. Walshe. *Nature and Treatment of Cancer*, London, 1846 92
2. Lage. *Krebshafte Entartung eines grossen Theils des Dickdarms.* Schmidt's Jahrbuch, 1847. lv, 295.
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Oesophageal transection for variceal haemorrhage

Sir

Jenkins and Shields (*Br J Surg* 1989; **76** 49–51) correctly question the efficacy of emergency oesophageal transection in patients with compromised liver function who failed sclerotherapy Mortality in their patients with poor liver function (Child's C) was 100 per cent, while half of Child's B grade patients died. The authors do not, however, define sclerotherapy failure nor does the data allow an accurate assessment of the number of acute injections attempted or the delay prior to an extensive devascularization of the lower oesophagus and proximal stomach.

The limitations of repeated injection sclerotherapy in continued acute variceal bleeding have previously been emphasized by our group[1]. The mortality rate in a small subgroup of patients (12 of 66) who required more than two injection sessions for control of bleeding was 66 per cent and a prohibitive 89 per cent when Child's A patients were excluded. This was significantly higher than the 21 per cent mortality rate in the group who stopped bleeding after one or two injection sessions. Further analysis failed to identify factors which predicted continued bleeding. These results stressed the limitations of repeated sclerotherapy in controlling continued variceal bleeding, and raised the unresolved question of how best to manage these patients.

The extensive devascularization procedure used by Jenkins and co-workers may explain the poor results achieved in this study and one may speculate whether a lesser procedure, such as simple oesophageal transection, would have been better tolerated Data on this issue are urgently needed. However, the decision to operate on these poor-risk patients is often difficult, bearing in mind their dismal prognosis even when control of variceal bleeding is achieved. This poses the difficult ethical question of when treatment should be withdrawn in selected patients. In this respect a prognostic index may be helpful in selecting patients for further active treatment.

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1. Bornman PC, Terblanche J, Khan D, Jonker MAT, Kirsch RE. Limitations of multiple sclerotherapy sessions for acute variceal bleeding. *S Afr Med J* 1986; **70**: 34–6.

Outpatient paediatric surgery

Sir

With reference to the article on outpatient inguinal hernia repair in children by Mr Mejdahl and colleagues (*Br J Surg* 1989; **76**: 406–7), it may be appropriate to commemorate the 50th anniversary of a forgotten pioneer article in this field. In 1938, Gertrude Herzfeld[1], surgeon to the Royal Edinburgh Hospital for Sick Children, reviewing her experience with 1000 inguinal herniorraphies in children, stated· 'It is important in operating on young infants not to keep them in hospital. A baby taken suddenly from its home environment, however bad, invariably loses weight, and is upset by admission to hospital. It is my usual practice to send the baby home some 2 hours or so after operation, and I have never had cause to regret this procedure'

Taking into account the progress made since that time and a personal experience of 4000 outpatient paediatric hernia repairs and appendicectomies[2], we consider the time ripe to propose appendicectomy as an additional day-care procedure In our own series of 1921 outpatient appendicectomies the readmission rate was 1·2 per cent for wound infection, fever and stool problems. Relaparotomy became necessary in three cases, mortality was nil. As a rule, complications of appendicectomy should not occur before postoperative days 3 to 7, by which time many children have already been discharged.

Surgeons have been slow following the concepts of Herzfeld's report. Day-stay appendicectomy will require surgical and anesthesetic techniques, preoperative and postoperative examination, patient selection, instruction and follow-up service in excess of routine standards. Outpatient paediatric surgery provides a stimulus to strive for professional and humane competence

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1 Herzfeld G. Hernia in infancy *Am J Surg* 1938; **39** 422–8.
2. Kux M, Ritz W, Fuchsjäger N, Baraka A. Tageschirurgie im Kindesalter· 4051 Eingriffe aus den Indikationen Appendizitis, Hernie, Phimose. *Akt Chir* 1986; **21**. 16–18.

Book reviews

A Colour Atlas of Faecal Incontinence and Complete Rectal Prolapse

M. M. Henry and N. H. Porter. 267 × 203 mm. Pp. 57 Illustrated. 1988 London. Wolfe Medical Publications Ltd. £19.00.

This is one of a series which sets out to illustrate single operations. In this case, three operations are covered, postanal repair, external anal sphincter repair and the Ivalon sponge repair for total rectal prolapse. The atlas is predominantly an illustration of the operations, step-by-step.

The photography and illustrations of postanal repair and external sphincter repair are quite remarkable for their clarity in what is a difficult area The standard of illustration is not as good for the Ivalon sponge repair, which makes it difficult to follow this operation The whole book is beautifully produced and doubtless will be welcomed by those collecting this series

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Chronic Pain

R. D. France and K. R. R. Krishnan. 152 × 241 mm. Pp. 542 Not illustrated. 1988. Washington, DC. American Psychiatric Inc £19.50.

This book is written by two American psychiatrists primarily for American psychiatrists with an interest in pain. Its purpose is to cover the subject from basic science to clinical management with an emphasis on psychological aspects. The book fulfils this aim and psychiatrists and clinical psychologists working in this field would find much of interest in it. It also covers drug therapy, physiotherapy, physical therapies such as nerve blocks and electrical stimulation, and the nursing of patients with chronic pain problems. The book gives emphasis to 'Multi-disciplinary Evaluation and Multi Modal treatments'. Unfortunately the results of such a grand design are assessment procedures and management programmes of such complexity that they are relevant only to highly specialized centres and are far too time-consuming for the average doctor who only sees a few patients with chronic pain every year This is not a book for the average doctor who wishes a short succinct introduction to the subject of chronic pain.

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Lives of the Fellows of the Royal College of Surgeons of England 1974–1982

E. H. Cornelius, S. F. Taylor. 240 × 155 mm. Pp 429. 1988. London: Royal College of Surgeons of England. £35.00.

In the 8 years from 1974 to 1982 the College lost its reigning President, Sir Alan Parks, and three past Presidents: Sir Cecil Wakeley, Sir James Paterson Ross and Lord Brock. Deceased Honorary Fellows included HRH the Duke of Gloucester, the Marquess of Exeter, and such distinguished overseas surgeons as John Cid dos Santos, J. Englebert Dunphy, John Loewenthal, Wilder Penfield, Pietro Valdoni and Owen Wangensteen. In our Fellowship before those years, there were many household names in surgery, who many will remember with affection.

Younger men of distinction were taken, too. The long list of men we knew, and others whose lives after diploma day are less fully recorded, are all here and each with a careful, thoughtful tribute. The editors have worked kindly and well to set this fine memorial to our colleagues who are gone ahead

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Surgical Pathology. 2nd ed.

W. Coulson. 178 × 254 mm. Illustrated. 1988. Philadelphia J. B Lippincott Co. £125.00.

This is a large, two-volume book with approximately 1700 pages. It deals with surgical pathology from the point of view of the histopathologist. It is copiously illustrated with well-produced photomicrographs, which are all in black-and-white.

Dr Coulson has written a number of the chapters but has drawn widely on his colleagues in pathology, especially those from Los Angeles, to write individual chapters. The overall standard is good but some subjects are dealt with rather superficially, which is surprising for a book of such length.

This is a book for the pathologist, written by pathologists, and it may find its way into departmental libraries in pathology departments It is certainly not the type of book which would be bought by practising surgeons, though they may occasionally wish to use it as a source of reference, particularly since the reference section in each chapter is very full.

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Manual of Surgical Therapeutics. 7th ed.

R. E. Condon, L. M. Nyhus. 220 × 135 mm Pp. 417. Illustrated. 1988 Boston· Little, Brown & Co. £9.95.

This book offers rapid access to a large variety of surgical problems encountered in both the emergency and elective situations. I enjoyed reading it thoroughly and feel it is relevant to all surgeons in training, especially to those who have to deal with emergencies.

The book has many authors – all contributing towards their own specialities in this manual. I think there is a genuine need for a book which does concentrate on the surgical therapeutics with regard to non-operative management of surgical patients. As stated in the Preface, the book is not meant to be a complete or systemic representation of all of surgery but instead the aim is to bring together in one volume all the material that is needed for quick review by surgeons faced with the clinical problem when there is not time to do otherwise

Generally speaking, I think this is a valuable contribution to medical education and the practice of surgery.

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Atlas of CO_2 Laser Surgical Technique

I Lanzafame 203 × 279 mm Pp. 286. Illustrated. 1988 St Louis Ishiyaku EuroAmerica Inc. $145 00

Most surgeons have wondered at some time during the 20 years that CO_2 lasers have been available if they would have a use for such an instrument in their operating theatre. Much of the literature about lasers is anecdotal and unsubstantiated, so surgeons understandably feel they need to see the instrument in use before they can make a decision This can be difficult to arrange, so a substitute is provided by this book with its large format and 400-plus photographs of lasers being used for a wide range of operations in general surgery together with pictures of the results. There are also sections on physics, safety, detailed descriptions of the techniques and extensive references

Liver resection is the principal operation for which surgeons wish for something better than the scalpel. Unfortunately, however, here the CO_2 laser fails to deliver, for that is the only operation that the authors accept is better done by conventional methods. For each of the other operations a list of advantages of the laser is set out, and these include greater precision of cutting, less blood loss, sterilization of infected tissue, efficient killing of malignant cells (therefore less tumour recurrence), sealing of lymphatics and less postoperative pain. This sounds impressive but is mostly unproven.

The disadvantages of laser surgery are not mentioned in this book, which is written by American enthusiasts. These are that the operations take longer, the instruments are awkward to use, there are possible dangers to patient and staff, they produce smoke, and they are expensive. Also, is the blood loss in most of the operations mentioned really a problem, can infected lesions not be as effectively dealt with by other methods today, is local recurrence significantly reduced and are the scars as good with the laser? Enthusiasts overlook such questions.

Will general surgeons wish to use lasers after reading this book? Those who have already decided to start laser surgery will obtain useful hints from this book, but most general surgeons will not be encouraged to change. However, it is easy to become complacent about such matters as blood loss and postoperative pain, and if the stimulation of seeing this new technique does not result in a change to using the laser, at least it should encourage a reassessment of present results in these areas to make sure that the existing techniques cannot be bettered.

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Outpatient Surgery

G. J. Hill. 178 × 267 mm. Pp. 696. Illustrated 1988. Philadelphia: W. B Saunders. £37.50.

That this book is in a third edition reflects the vigour of the North American movement to day-case (ambulatory) surgery and technical procedures. The book is written by a galaxy of distinguished authors, all but one of whom are from North America.

The book is eclectic with an interesting mixture of topics reflecting American rather than European practice and organization Somehow I sensed that the generalist is rather more alive in some American situations than in the UK. Because each section is written by specialists there are inevitable overlaps and repetitions; indeed, some of these territorial inexactitudes probably represent demarcation disputes! But they also give alternative views of commonplace problems, for example suturing a full thickness eyelid wound, which require special technical care Demarcation disputes are not always malign and in this book represent pride in individual specialities rather than atavism.

The book crosses the Atlantic well and will be useful in many of our hospitals; your hospital copy will be best kept as a bench book close to the Accident and Emergency operating room. Overall, however, the book does fit the American more easily than the contemporary UK scene, though no doubt in 20 years our practice will be similar to that in America today. I quote.

> The spectrum of (day-case) surgical procedures thus ranges from skin biopsies in the physician's office to cholecystectomy performed in the hospital.

Day-case inguinal herniorrhaphy is still considered too adventurous for many British surgeons; obviously the NHS budget still has too much fat in it . . or does humanity still outweigh economics in British surgeons' morality?

I recommend this as a good, sensible and comprehensive text about outpatient surgery, just as the title suggests.

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Erratum

'Antibiotic prophylaxis and postoperative sepsis after cholecystectomy' by D. Menzies and H. Ellis, *Br J Surg* 1989; **76**: 764, Table 1. The headings in this table were all displaced one position to the left. We apologize for this error. The letter is reproduced in full below.

Antibiotic prophylaxis and postoperative sepsis after cholecystectomy

Sir

The article by Wells *et al.* (*Br J Surg* 1989; **76**: 374–7), concerning the relationship between bile colonization, high-risk factors and postoperative sepsis, mirrored the results of a consecutive series of 504 cholecystectomies from the Westminster Surgical Unit[1] (*Table 1*).

Table 1 *Bile infection and wound infection in a consecutive series of 504 cholecystectomies*

	Positive bile culture	Positive bile culture with wound infection	Same organism in bile and wound infection	Negative bile culture with wound infection	Negative bile culture with *S. aureus* wound infection
Prophylactic antibiotics ($n=379$)	79/379 (21)	12/79 (15)	8/12 (66)	14/300 (5)	9/14 (64)
No antibiotics ($n=125$)	21/125 (17)	9/21 (43)	5/9 (56)	23/104 (22)	16/23 (69)
Significance (χ^2)	—	$P<0.01$	—	$P<0.001$	—

Values in parentheses are percentages

Wells *et al.* conclude that, despite prophylactic antibiotics, bile colonization remains the major factor associated with postoperative sepsis This is in agreement with our results They did not compare their study group with a control group, justifiably, in view of the current body of evidence that demonstrates the value of antibiotics in biliary surgery

In our own analysis the most common cause of wound infection was *Staphylococcus aureus*, not biliary organisms, for those patients receiving no prophylaxis In those patients who received antibiotic prophylaxis, the incidence of *S. aureus* wound infections was significantly reduced

We would suggest that it is because of, not despite, antibiotics that bile colonization is the major factor associated with postoperative sepsis. This is more in line with the study by Willis *et al.*[2] who showed that in the absence of prophylactic antibiotics (*not* in the presence of prophylaxis, as quoted by Wells) wound infections were more commonly exogenous, a finding confirmed by Van Leeuwen[3].

It is because of this that we would agree with Wells in concluding that selective administration of antibiotics is inadvisable, and would add that, in choosing a suitable antibiotic, one should be chosen that has an anti-staphylococcal activity

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1. Menzies D, Ellis H. *Staphylococcus aureus*—a major cause of post-cholecystectomy wound infection. Paper presented at the 2nd world congress on Hepato-pancreato-biliary surgery, Amsterdam, June 1988
2. Willis RG, Lawson WC, Hoare EM *et al* Are bile bacteria relevant to septic complications following biliary surgery? *Br J Surg* 1984, **71**. 845–9.
3. Van Leeuwen PAM, Keeman JN, Butzelaar RJM, Van Den Bogaard AEJM Correlation between a positive gallbladder culture and subsequent wound infection after biliary surgery A retrospective study of 840 patients *Neth J Surg* 1985; **37**· 179–82

Notices and announcements

15–18 October 1989
38th Annual Meeting of Brazilian Society of Coloproctology
Rio de Janeiro, Brazil
Information. The Chairman, Ronalvo Ribeiro, Avenide Mem de Sá, 197, Rio de Janeiro, Brazil, CEP 20230

15–20 October 1989
American College of Surgeons 1989 Annual Clinical Congress
Atlanta, USA
Information· Sally Garneski or Susan Krasnow, American College of Surgeons, 55 East Erie Street, Chicago, Illinois, USA

15–21 October 1989
Recent Advances in Pancreaticobiliary Surgery
Edinburgh, UK
Information. Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

16–19 October 1989
2nd International Conference on Melanoma
Venice, Italy
Information General Secretariat, 2nd International Conference on Melanoma, c/o Isituto Nazionale Tumori, Via G. Venezian 1, 20133 Milan, Italy

17–20 October 1989
Progress in the Investigation and Management of Venous Problems
London, UK
Information. Miss A. Taft, Conference Officer, Vascular Surgery, 10th Floor, QEQM Wing, St. Mary's Hospital, London W2 1NY, UK

20 October 1989
Symposium. **Claudicants: where do the Goal Posts Stand?**
Bath, UK
Information: Dr A Chalmers, Consultant Radiologist, Royal United Hospital, Combe Park, Bath BA1 3NG, UK

23–25 October 1989
International Symposium – The Biology and Clinical Applications of Interleukin 2
Sheffield, UK
Information Robert Rees, Department of Virology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK

25 October 1989
Pre-operative Clinical Cardiac Examination and ECG are Adequate Pre-Operative Assessment for Arterial Surgery
London, UK
Information· Mr John Wolfe, Vascular Surgery Unit, St Mary's Hospital, Praed Street, London W2 1NY, UK

6 November 1989
How to Write a Surgical Paper
London, UK
Information: Mary Wheaton, Hunterian Institute Office, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

6–10 November 1989
MR Physicians Seminar: "Magnetic Resonance Imaging; Techniques and Imaging Methodology"
Philadelphia, USA
Information: Janice Ford, CME Coordinator, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia PA 19104, USA

6–10 November 1989
Annual Course in Advanced Hepatobiliary and Pancreatic Surgery
London, UK
Information. Wolfson Conference Centre, Royal Postgraduate Medical School, Du Cane Road, London W12 0NN, UK

7–10 November 1989
The Second British Symposium on Total Knee Replacement
Harrogate, UK
Information. Metaphor Conferences and Meetings, 21 Kirklees Close, Farsley, Pudsey, West Yorkshire LS28 5TF, UK

8–11 November 1989
Endocrine and Nonendocrine Producing Tumours 33rd Annual Clinical Conference
Houston, Texas, USA
Information. Office of Conference Services, MD Anderson Cancer Centre, 1515 Holcombe Blvd, Houston, Texas 77030, USA

12–17 November 1989
International College of Surgeons 16th European Federation Congress
Jerusalem, Israel
Information. Professor Arye L. Durst, The Secretariat, PO Box 983, Jerusalem, Israel

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information: J. P. Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

16–19 November 1989
3-D Imaging in Medicine
San Diego, California, USA
Information Ms Janice Ford, CME Coordinator, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104, USA

17–19 November 1989
Eighth Annual Trauma Symposium
El Paso, Texas, USA
Information: William Beaumont Army Medical Center, El Paso, Texas 79920, USA

18–22 November 1989
9th Biennial Asian Congress on Thoracic and Cardiovascular Surgery
Taipei, Taiwan, Republic of China
Information The Secretariat, The 9th Biennial Asian Congress on Thoracic and Cardiovascular Surgery, PO Box 68–439, Taipei, Taiwan, Republic of China

23–24 November 1989
Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland
Dundee, UK
Information Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

3–9 December 1989
Breast Cancer: New Developments in Biology, Diagnosis and Treatment
London, UK
Information· Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information Dr Joseph W. C Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

19–21 January 1990
26th Head and Neck Course
Liverpool, UK
Information Professor P. M Stell, Dept of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, UK

20–21 January 1989
Hong Kong Surgical Forum
Hong Kong
Information Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

4–10 March 1990
Cancer in Children
London, UK
Information: The British Council, Courses Department, 65 Davies Street, London W1Y 2AA, UK

11–13 March 1990
2nd Surgical Masterclass of the Royal College of Surgeons of Edinburgh
Aviemore, UK
Information Mrs Maureen Webb, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

28–30 March 1990
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Cardiff, UK
Information. The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

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The American Journal of Surgery

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The Society for Clinical Vascular Surgery
The Society of Head and Neck Surgeons
The Southwestern Surgical Congress
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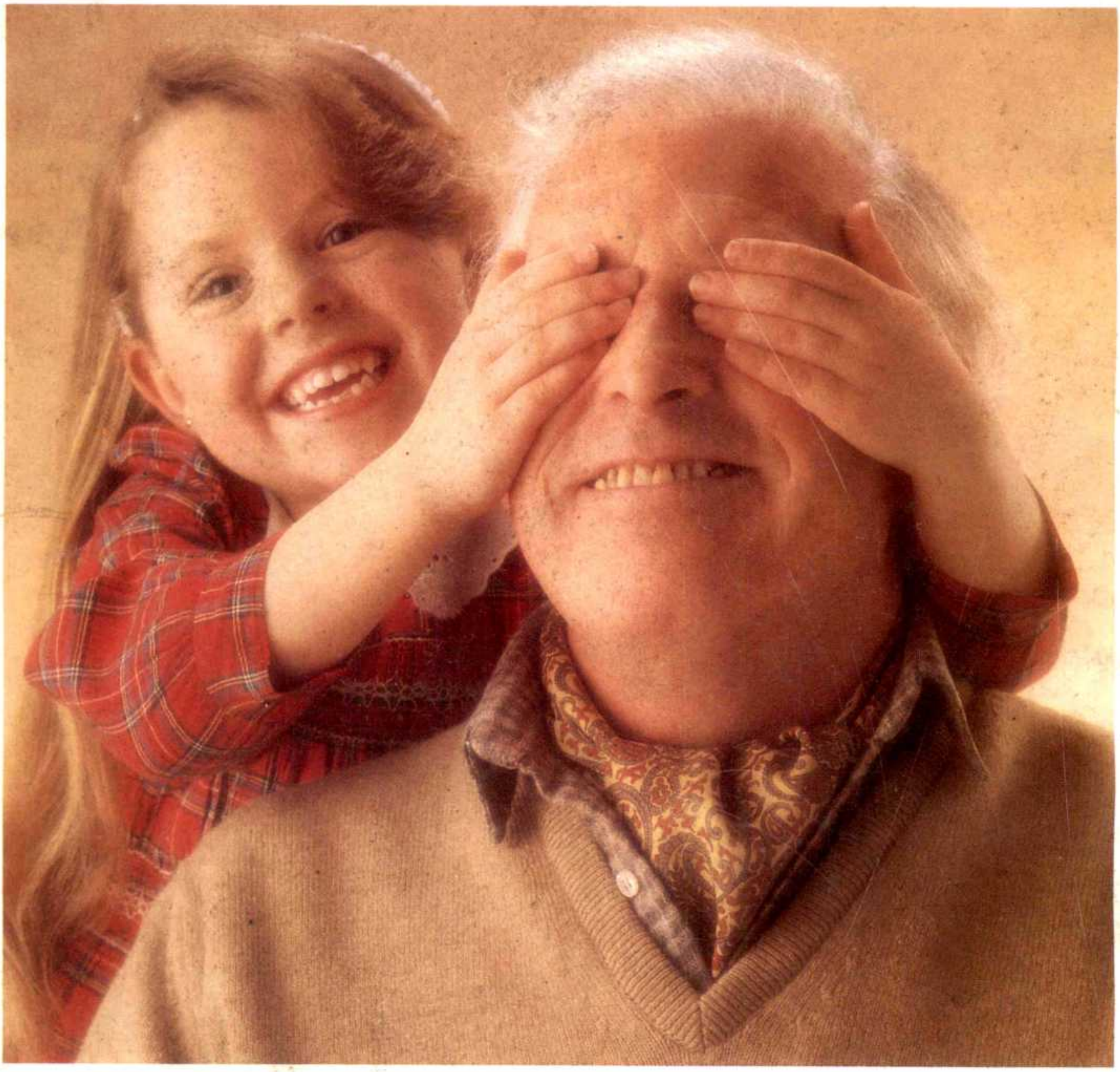
Guess which prostate cancer treatment most patients would choose.



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Reference 1. Lunglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex'– a new treatment for prostatic cancer. International Congress and Symposium Series.* 125. London: RSM Series, 1987: 47-51.
2. Peeling W B. ibid: 27-46.

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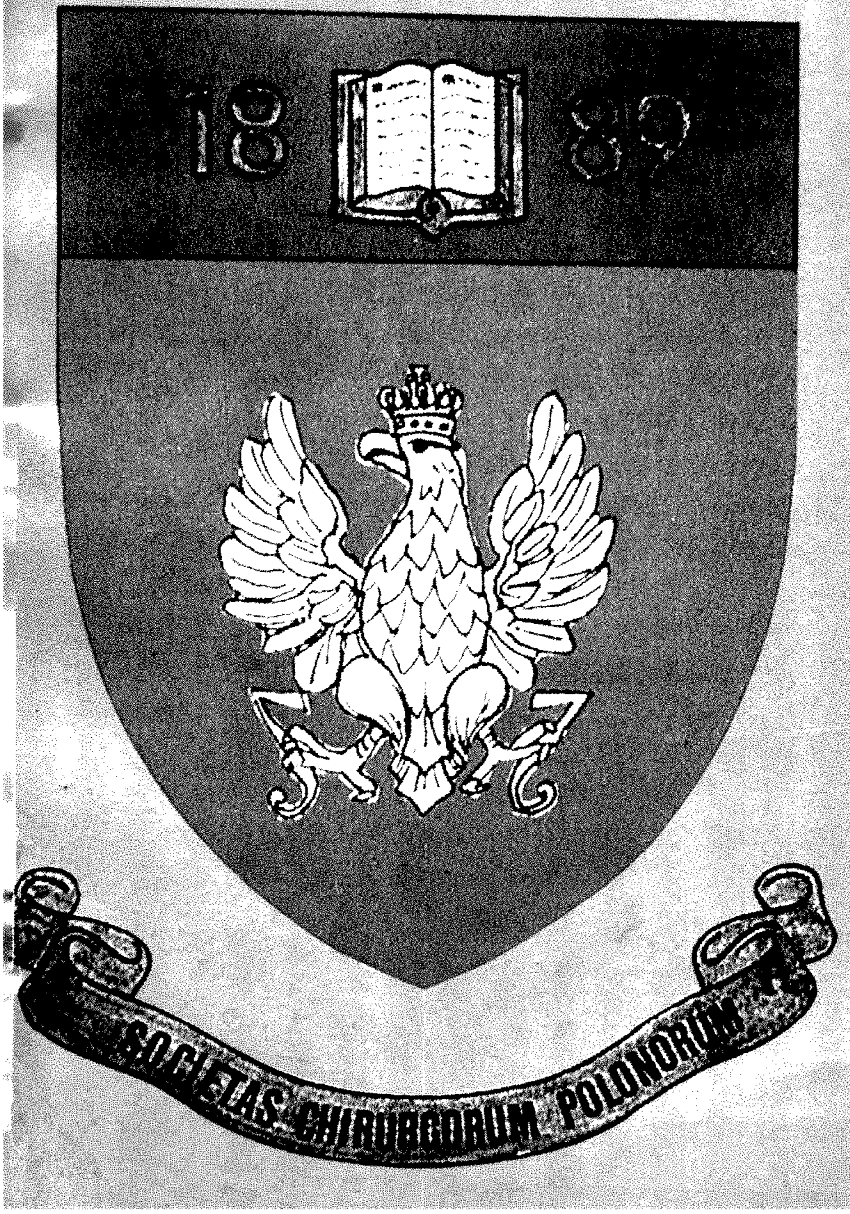

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R. J. A. M. van Dongen, University of Amsterdam (Eds.)

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The Centenary of the Polish Association of Surgeons and the Bicentenary of the Academic Surgery in Poland

Academic surgery in Poland had its beginnings in the Chair of Anatomy, Surgery and Obstetrics founded in the Jagiellonian University, Cracow in the late 18th century. The Jagiellonian University was founded in 1364 in Cracow, then the capital of Poland. The University flourished throughout the Renaissance and among the greatest graduates of the Medical Faculty was Mikołaj Kopernik (1473–1543), famous physician and astronomer. The importance of the University declined when the capital was effectively moved to Warsaw by King Sigismund III in 1609. However social and cultural reforms in the mid-18th century led to the creation in Poland of the first European Ministry of Education. The consequent re-invigoration of the Jagiellonian University led to the establishment of the Department of Surgery under the supervision of Professor Rafał Czerwiakowski (1743–1816).

Czerwiakowski was not only an outstanding surgeon but an important teacher who introduced the autopsy to clinical teaching and who also wrote a textbook of surgery and numerous research papers. The most splendid development of the University Department of Surgery was initiated by Ludwik Bierkowski (1801–1860) who used ether anaesthesia for the first time in Poland on 6 February 1847. This very talented educator developed the teaching of surgery, and compiled and wrote an atlas of anatomy, a textbook of surgical techniques and numerous papers in which he devoted much attention to medical ethics. His successor, Antoni Bryk (1820–1881), pioneered antiseptic surgery in Poland. Following Bryk, Jan Mikulicz-Radecki (1859–1905), a favourite student of Billroth, was appointed Professor.

Professor Mikulicz's arrival in Cracow evoked certain anxiety, as he was reputed to have an 'incorrect command of the Polish language'. Yet in his inaugural address Mikulicz emphasized that '... a faculty of poor knowledge of the Polish language is charged upon me; yet this language is the mother tongue for me and for all of you gentlemen alike ...'[1]. During his tenure of the Chair in Cracow, Mikulicz invented new operative techniques and designed surgical equipment and instruments which are still in use today. He applied a new technique of gastric resection and in February 1887 performed pyloroplasty, known as a Heinecke-Mikulicz method. In Cracow he invented alimentary tract endoscopy, laying the foundations for the modern gastroenterological diagnostics and was the first to describe the endoscopic image of effectively treated gastric cancer[2], and became known as the 'father of alimentary tract endoscopy'. His endeavours to fund a new building for the Department were abortive, so in exasperation he resigned and moved to Krolewiec and later to Wroclaw.

His equally famous successor Ludwik Rydygier (1850–1920), appointed in 1887, had gained world renown on 16 November 1880 when he performed a gastrectomy in a patient with gastric cancer, thus becoming the second surgeon to do so after Pean and preceding Billroth. On 21 November 1881 he was the first to resect part of the stomach for peptic ulcer, paving the way for the routine surgical management for acid/pepsin disease.

His pioneering method, opening the possibilities for peptic ulcer surgery, initially did not find any followers, and was not given a proper credit in the literature. It was commented with a single statement: 'and hopefully, the last'[3]. Rydygier was the first surgeon ever to employ gastroenterostomy for ulcer pyloric stenosis on 13 March 1884 and introduced important new methods in biliary, vascular and urological surgery while in Cracow. He succeeded in his efforts to obtain permission to build new premises to house the Department. The construction work took less than a year and, in October 1889, the first Congress of Polish Surgeons was organized simultaneously with the opening of the Department. Rydygier was active in Cracow for 10 years, and later he and his entire team of assistants moved to Lvov where he was appointed to the Chair of Surgery at the local university.

Alfred Obaliński (1843–1898), the immediate successor to Rydygier, became famous for being the first surgeon to use the Giglic saw in cranioplasty[4]. He was also the first surgeon in Poland to present, on 11 February 1896, a radiograph of a dislocated elbow made in the laboratory of Professor Olszewski from the Jagiellonian University who, in 1888, condensed oxygen and nitrogen together with Professor Wróblewski. Obaliński was succeeded by Bronislaw Kader (1863–1937), a student of Mikulicz.

Chairs of Surgery were also being organized in other places. The Department of Surgery was founded in Vilnius in 1783, and in Warsaw in 1809; however both these centres existed only until the early 19th century.

In 1857 the Medical-Surgical Academy was established in Warsaw and in 1862 it became the Faculty of Medicine of the Warsaw Szkola Glowna. The most prominent Warsaw surgeons of the last century included Aleksander Le Brun (1803–1868), Polikarp Girsztoft (1827–1877), Hipolit Korzeniowski (1827–1879) and Julian Kosiński (1833–1914). A new surgical centre started flourishing in Poznań and the most famous surgeon of that time was Tomasz Drobnik (1858–1901).

When after World War I Poland regained independence, new horizons opened for the development of surgery. To the existing centres in Cracow, Warsaw and Lvov new ones were added in Vilnius where the University was re-opened and in Poznań following the establishment of a university there. In Vilnius surgery was headed by Professor Kornel Michejda (1887–1960) and in Poznań by Professor Antoni Jurasz (1882–1961), the author of the innovative method of pancreatic cystogastrostomy. The most famous Warsaw surgeons of that time were Antoni Leśniowski (1867–1939) and Zygmunt Radliński (1874–1941), and Hilary Schramm (1857–1940) and Tadeusz Ostrowski (1881–1941) in Lvov.

In Cracow Maksymilian Rutkowski (1867–1947) was appointed Professor of Surgery. He developed numerous surgical methods and encouraged expansion of various surgical specializations, e.g. orthopaedics, urology, neurosurgery, thoracic and cardiac surgery. Rutkowski was himself a pioneer of oesophageal surgery, developing oesophagectomy with replacement of the removed segment by the mobilized stomach drawn up through the chest using the Rutkowski, Lortat-Jacob method[5].

Further development of surgery in Poland ground to a halt with the outbreak of World War II. All the university schools were closed and the Professors sent to concentration camps. When open training of medical personnel was impossible in the occupied country, the Polish Faculty of Medicine was established at the University of Edinburgh with Professor Antoni Jurasz from Poznań as its Dean.

After World War II favourable conditions for academic surgery were created in the Polish People's Republic, first in the reopened universities and subsequently in ten Medical Academies functioning under the Ministry of Health. Pre-war Professors or their former students were appointed and they carried on the tradition established by the founders of the Polish School of Surgery and contributed much to the education of a vast number of surgeons, both general and representing various specialties such as orthopaedics, urology, neurosurgery, thoracic, paediatric, cardiac and vascular surgery.

Rydygier was the driving force behind the first Congress of Polish surgeons held in Cracow in October 1889. Surgeons from all the territories of the former kingdom of Poland participated, a constitution for the Society was drawn up and a membership register of over 200 created. Rydygier was elected the lifelong President of the Society and presided over the annual Congress held every year until World War I. Because Poland was partitioned between Russia, Prussia and Austria, the title Polish Association of Surgeons could not be adopted until 1921 at the first Congress held at Warsaw, now the capital of an independent Poland. At the 1921 Congress a resolution stressing the continuity of the Association with the previous Congress was unanimously approved. The Council of the Polish Association of Surgeons organized the VIII Congress of the International Society of Surgery in Warsaw in 1929. Since 1922 the Association has published the journal *Polski Przegląd Chirurgiczny*. During World War II the German occupation permitted no collective activities of the Polish Association of Surgeons.

The aims of the Association include the application of scientific progress in surgery, promotion of research in experimental and clinical surgery, cooperation in the organization of public health care and postgraduate education, and training of surgeons and representatives of Polish surgery at home and abroad.

National Congresses of the Polish Surgeons were held annually until 1952 and since then have been held every second year. Each has about 1000–1500 participants. The sections of the Society of Polish Surgeons organize, every second year, scientific conferences with participation of foreign guests, and the Society holds monthly scientific meetings. The Association is a member of the International Federation of Colleges of Surgeons.

The Centenary Congress of the Association will be held in Cracow in September 1989, a meeting which also celebrates the Bicentenary of the University Department of Surgery of the Jagiellonian University. The President of the Congress, Professor of Surgery in Cracow, is Professor Tadeusz Popiela.

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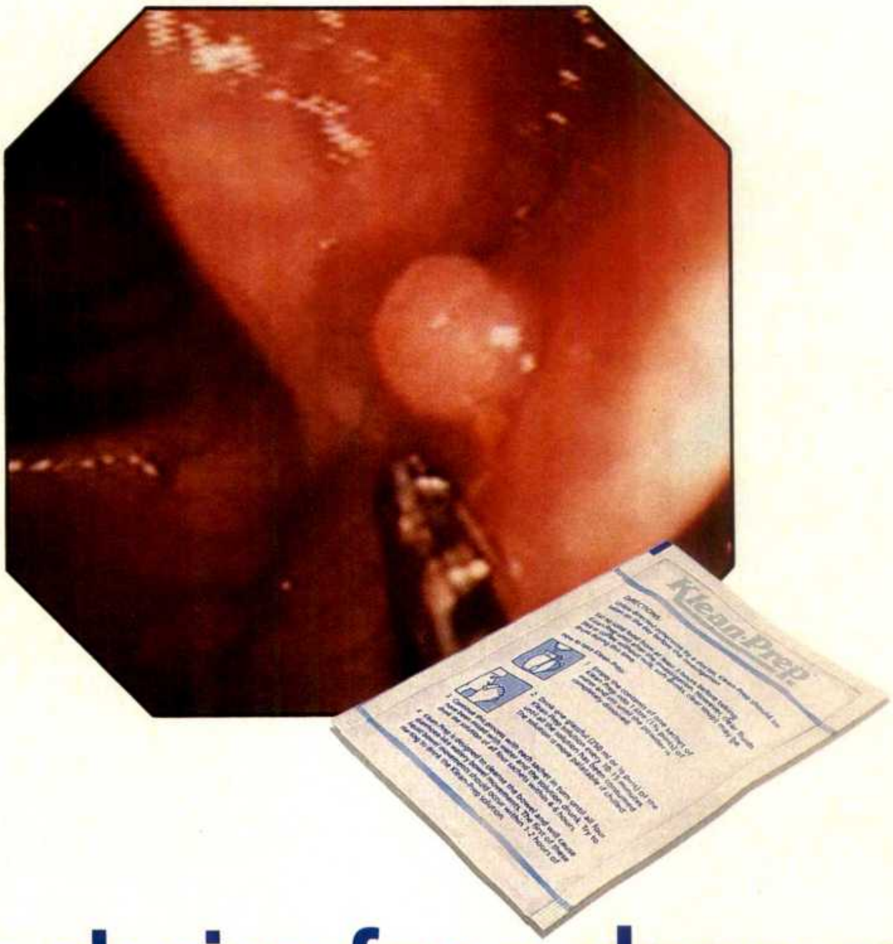

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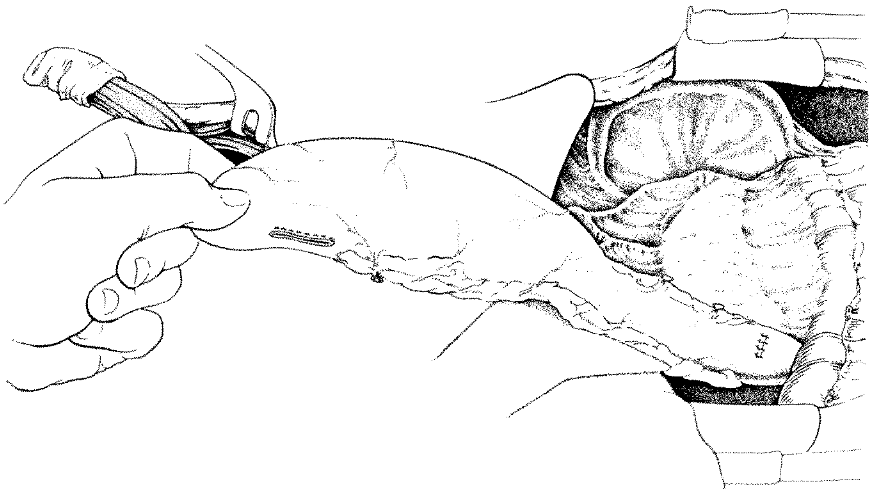

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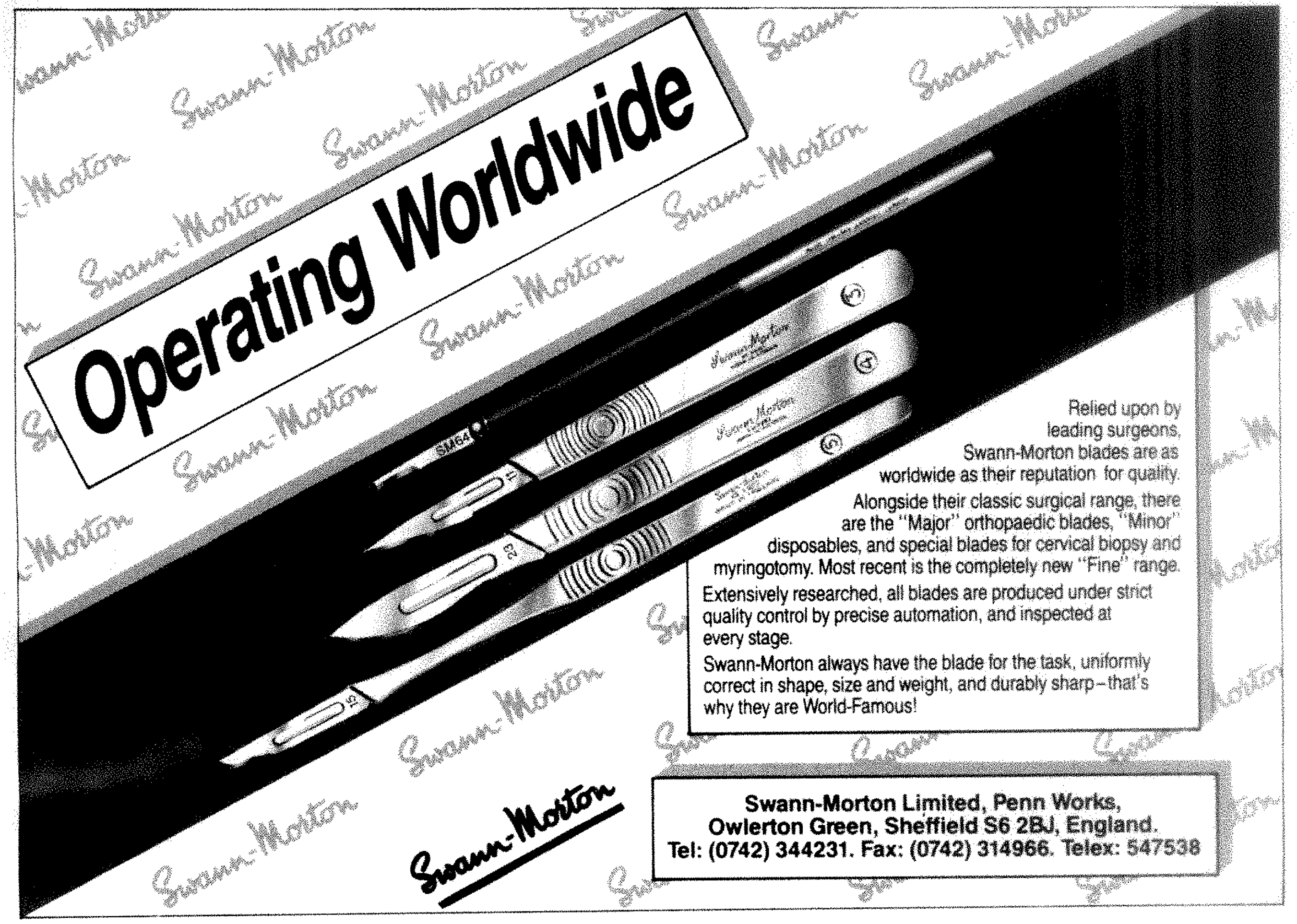

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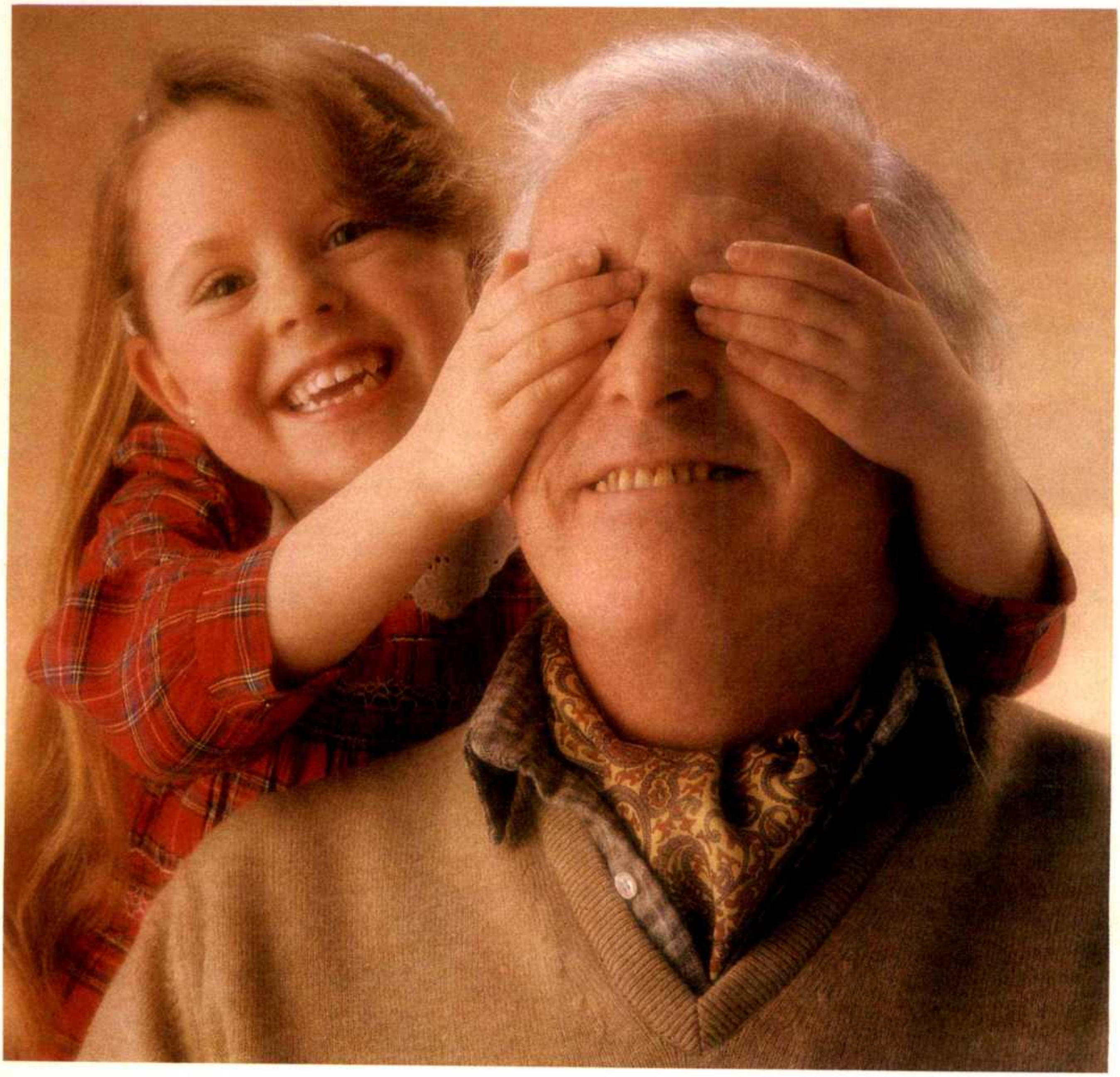

In a recent study[1], 57 prostate cancer patients were invited to participate in choosing their treatment. All were informed that the two treatments available, sub-capsular orchidectomy or 'Zoladex', were similar in efficacy and side effects. 49 of the patients (86%) opted for 'Zoladex'.

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Br. J. Surg. 1989, Vol. 76, November, 1107–1108

Perioperative anticoagulant control

It is a common clinical dilemma to balance safely the opposing risks of thromboembolism and haemorrhage in anticoagulated patients undergoing surgery. In the Hastings District, with a population of only 170000, two anticoagulated patients per month face surgery. A clear policy, kept under regular review, is therefore advisable but detailed advice on the anticoagulant control of such patients undergoing surgery is lacking.

It appears to be safe to discontinue anticoagulation for 6 days before and during non-cardiac surgery. No thromboembolic complications occurred after 180 operations on 159 patients with cardiac valve prostheses although 13 per cent experienced difficulties with haemostasis[1]. However, two patients with prosthetic mitral valves died from thromboemboli following a similar regimen[2], with four episodes of haemorrhage in another nine patients whose anticoagulants were continued. Some authors recommend replacing warfarin, whose mean(s d.) plasma half-life[3] is 37(15) h, with heparin until 6 h before the operation and restarting both after 36 h or less[4,5]. The use of postoperative heparin for those at highest risk is supported by evidence that intracardiac thrombi begin to form within hours of cardiac surgery[6]. Additional antiplatelet therapy reduces thromboemboli from prosthetic valves because platelet accretions may occur despite adequate anticoagulation. It is probably safe to continue warfarin during dental[4] or cataract[7] surgery, but opinion differs for regional anaesthesia[5] and central venous cannulation.

Guidelines should be simple but flexible. The aim is to achieve an international normalized ratio (INR)[8] of $<1{\cdot}5$ at the time of surgery, keeping the duration of subtherapeutic anticoagulation to a minimum and restoring full anticoagulation as soon as the risk of postoperative haemorrhage allows. Albumin binding and the resynthesis of coagulation proteins govern the rate at which normal coagulation is restored after stopping warfarin. This is 3–5 days as a rule but the metabolism of warfarin varies so that individual requirements must still be tailored to the INR and type of surgery. Vitamin K is best avoided because of difficulty in regaining control after its administration, although low-dose regimens (2·5 mg oral phytomenadione for 2 days before surgery[3]) have been advocated while continuing warfarin. For surgical emergencies in any anticoagulated patient, fresh frozen plasma should be used to reduce the INR to $<1{\cdot}5$.

Anticoagulated patients can be broadly divided into those with mechanical prosthetic valves and those receiving warfarin for any other reasons, such as venous thrombosis, pulmonary embolus or ventricular aneurysm. Elective procedures in the latter group should be delayed if possible until anticoagulant therapy has been completed. Patients should understand the increased risks of surgery and it may be helpful to compare these risks with those of spontaneous haemorrhage (1 per cent per patient-year[9]) or thromboemboli (3 per cent per patient-year[9]) for those with mitral prostheses who never have another operation.

Patients with prosthetic valves should be admitted on the day that warfarin is to be stopped, 3 days before surgery. The INR should be checked on admission. That evening, 24 h after the last dose of warfarin, intravenous heparin (initially 15000 units/12 h) should be started. The activated partial thromboplastin time should be checked 12 h later, aiming for 70–100 s. Heparin should be stopped 6 h before operation, and both the INR and activated partial thromboplastin time should be checked 1 h before surgery; consequently the operation is best scheduled last on a morning list or first in the afternoon. Surgery should be delayed or fresh frozen plasma used if the INR is $>1{\cdot}5$. The small but inevitable risks associated with any blood products warrant consideration in these circumstances. After the operation warfarin should be restarted as soon as the patient is taking oral fluids. Postoperative heparin is not required for patients with mechanical aortic valves unless the patient cannot drink for more than 48 h.

For those with mechanical mitral valves, two modifications are recommended because the risk of emboli is higher than with aortic prostheses. When warfarin is

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Helpful discussions with surgical colleagues, Dr D A. Chamberlain and Dr R P H Thompson, were appreciated.

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discontinued, 75 mg aspirin or 300 mg dipyridamole should be given daily. Six to 12 hours after the operation the heparin infusion should be restarted and continued until warfarin control is re-established. For short operations (less than 20 min) it may be preferable simply to use fresh frozen plasma, bearing in mind the associated risks.

Patients on anticoagulants for any reason other than for mechanical cardiac valves can have surgery after omitting three doses of warfarin. Routine admission the day before surgery is reasonable if appropriate instructions on omitting warfarin are included in the admission letter. The INR should be checked on admission and again before the operation. The preoperative dose of warfarin can be restarted with oral fluids. Where the risk of thromboembolism is considered particularly high (such as in patients with recurrent pulmonary emboli undergoing pelvic surgery), or when a delay of more than 48 h is anticipated before warfarin can be restarted, a postoperative heparin infusion would be appropriate.

Three days without warfarin, intravenous heparin for selected patients, antiplatelet therapy with mitral prostheses and a written policy form the basis of management. These practical guidelines need to be tailored to individual patients but may help junior staff who often have responsibility for anticoagulant control and also form the basis for discussion on this neglected subject.

S. Travis, R. Wray and K. Harrison

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Br. J. Surg. 1989, Vol. 76, November, 1109–1110

Restorative proctocolectomy is the first choice elective surgical treatment for ulcerative colitis

Proctocolectomy and an end ileostomy have remained the cornerstone of surgical treatment for ulcerative colitis throughout the last 50 years. Many patients owe their lives to this procedure. It eradicates the disease and restores the patient's well-being. All general surgeons are trained in its execution, and most understand its complications. It has stood the test of time, and recently has quite rightly been the preferred option when treating young patients with colitis. The price paid for cure, however, is high; an ileostomy may cause mechanical, psychosocial and sexual problems, the latter occurring despite an intersphincteric dissection of the rectum[1]. It is not surprising, therefore, that surgeons have striven to improve the quality of their patients' lives but until recently, their attempts to do so were far from satisfactory. Subtotal colectomy and ileorectal anastomosis was always regarded with scepticism, not least because of the high risk of carcinoma development[2]. Transformation of the end ileostomy to a continent Koch ileostomy has never become popular because it has a high failure rate[3].

Attempts to eradicate the disease yet restore gastrointestinal continuity and continence were for a long time regarded as laudable but conflicting objectives. It is therefore perhaps not surprising that the first report of mucosal proctectomy and ileoanal anastomosis in 1948 was received with surprise and perhaps a certain degree of incredulity. Ravitch[4] claimed that he could eradicate the disease by colectomy and rectal mucosectomy and achieve gastrointestinal continuity and continence by drawing the ileum down through the denuded rectal cuff and anastomosing it to the anal canal. The scepticism about his initial work was fuelled by other surgeons who were unable to reproduce his results. We had to wait 30 years until Martin and his colleagues in Cincinnati, using a modification of Ravitch's original operation, showed that mucosal proctectomy and ileoanal anastomosis was indeed feasible[5]. However, it rapidly became obvious that the operation had an Achilles' heel, namely frequency and urgency of defaecation. It was then that Sir Alan Parks, applying Koch's concept, created an ileal pelvic reservoir so as to increase the capacity of the neorectum[6]. This simple yet effective innovation considerably reduced the frequency of defaecation and converted the procedure from a merely feasible one into a practical alternative to proctocolectomy. Parks' first paper on the subject was in 1978, but 10 years later proctocolectomy still remains the procedure of first choice in most hospitals in the UK. Surgeons quite rightly tend to be conservative with a small 'c'; before an operation is accepted by the *corps chirurgie* it has to be shown to have stood the test of time. Is 10 years therefore a sufficient period to have elapsed for restorative proctocolectomy to have reached the status of the first choice elective procedure for most patients with ulcerative colitis?

There is no doubt that the last 10 years have seen considerable modifications to Parks' original operation. The procedure used to be tedious and technically demanding, the mucosectomy being mainly responsible for the difficulties. At first it was thought necessary to denude 10–12 cm of rectum, but gradually it was realized that the rectal cuff could be much shorter, no more than 4–5 cm. Not only did this simplify the procedure, but the modification reduced the incidence of cuff abscess and pelvic sepsis. Initially, Parks constructed a triplicated pouch with a long efferent spout, 5 cm in length. Half of his patients, however, failed to evacuate spontaneously; the elimination of the efferent spout virtually eradicated the problem. Configuration of the pouch has also undergone experimentation, the triplicated design being joined by the J (Reference 7) and more recently the W designs[8]. While the debate continues about the best design of pouch, all the data show that the greater the pouch volume the better the result in terms of frequency and urgency.

Several large series have now been published which, having incorporated some of the modifications discussed above, demonstrate the effectiveness of the procedure[9]. Thus most patients undergoing the procedure can now expect to be continent most of the time, have a frequency of about 6 bowel actions per 24 hr 6 months after ileostomy closure, delay defaecation for 30 min and retain normal bladder and sexual function. It is true that the operation has defects; many patients have to evacuate once during the night, some leak faeces occasionally and others have attacks

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of pouchitis which is akin to their previous colitis. Most patients, however, are very prepared to put up with these imperfections to avoid an ileostomy. If at the end of the day the disadvantages outweigh the benefits, an end ileostomy can still be constructed. It might be expected, therefore, that such an outlook would establish the operation as the first choice procedure. This has not yet occurred, probably because most surgeons still regard the operation as technically demanding, despite the modifications. The ground, however, has now shifted with the introduction of circular stapling instruments which have considerably simplified the procedure. Several techniques have recently been described[10–12]; and despite differences they are similar in principle. Thus, the rectum is dissected right down to the pelvic floor and cross-stapled using an appropriate transverse stapling instrument. A pouch is constructed either by hand or by a GIA® stapler (US Surgical Corporation and Auto Suture UK, Ascot, UK). The pouch–anal anastomosis is achieved by one of the circular stapling guns after first detaching the head and inserting the shaft through the wall of the closed anorectal stump. The new Premium CEEA® stapler (US Surgical Corporation and Auto Suture UK) is particularly useful in this regard. These techniques eliminate the need for a mucosectomy, shorten the procedure by about one hour and probably ensure a more secure anastomosis. They are also thought to inflict less damage on the anal sphincter than the conventional technique, although this is controversial[12]. Despite this considerable technical advance, there remains one problem: diseased rectal mucosa is left behind. However, provided the rectal dissection is taken right down to the pelvic floor, no more than 2–3 cm of residual anorectum above the dentate line should remain. The subsequent risk of neoplastic change must be very small, and surveillance of the region should be relatively easy. Even so, in the well-built male patient with a narrow pelvis in whom it may not be possible to dissect the rectum down to the pelvic floor, the conventional restorative proctocolectomy is probably more appropriate.

During the last 40 years, we have seen the operation of restorative proctocolectomy evolve from the experimental technique of Ravitch through the practical yet technically demanding procedure described by Parks to the relatively easily performed stapled pouch–anal anastomosis. The latter has taken the procedure from the specialized centres and placed it firmly in the ambit of most general surgeons with an interest in coloproctology. Many will argue, correctly in my view, that before embarking on the stapling procedure the surgeon should be trained in endoanal techniques in case he has to redeem a difficult situation. Since most surgeons with colorectal expertise possess these skills, there is little doubt that restorative proctocolectomy will and should be offered as the first choice elective operation to most young patients with ulcerative colitis who require surgical treatment.

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Primary disorders of oesophageal motility

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Primary motor disorders of the oesophagus have distinct manometric patterns but require full oesophageal investigation to exclude a secondary cause. Myotomy and forceful dilatation give good results in achalasia, though myotomy is superior in the long term. Indications for surgery are rare in diffuse spasm and nutcracker oesophagus. Non-cardiac chest pain may be related to reflux, diffuse spasm or nutcracker oesophagus, but correlation between motor abnormalities and symptoms is poor and psychological disturbances are frequent.

Keywords: Motility, oesophagus, achalasia, diffuse spasm, nutcracker oesophagus, gastro-oesophageal reflux, cricopharyngeus, manometry

Oesophageal motility disorders include a wide range of recognizable clinical entities and a variety of conditions in which the motor dysfunction cannot easily be classified. They may involve separately the upper oesophageal sphincter, the oesophageal body, or the lower oesophageal sphincter, but more than one region may be affected. Motor disorders are classified as primary when no underlying oesophageal or systemic disease influencing motility is present, or secondary when there is an identifiable oesophageal or systemic disorder. Manometric studies provide the objective evidence with which a clinical diagnosis can be confirmed, but radiographic, endoscopic and radionuclide investigation may also provide useful clinical information.

Upper oesophageal sphincter disorders

The high-pressure zone of the upper oesophageal sphincter corresponds closely to the anatomical position of the cricopharyngeus muscle. Manometrically it is 2–4 cm long and thus exceeds the anatomical length of the cricopharyngeus[1,2]. It is generally accepted that a portion of the inferior constrictor and possibly the upper oesophageal circular smooth muscle fibres contribute to the sphincter[3,4], although it is possible that the longer length on manometry may be artefactual[5]. One major problem limiting the usefulness of manometry in studying the upper sphincter is its axial asymmetry Failure to appreciate this makes many of the older studies of upper sphincter dysfunction of doubtful validity. Recently, modifications of sleeve sensors have been used successfully to record upper oesophageal sphincter function[6] These studies[6] demonstrate that the muscle is normally in a state of tonic contraction with a mean(s.d.) pressure of 40(17) mmHg There is little temporal variation in a given subject, and a range of 20–70 mmHg between subjects. The pressure increases towards the end of inspiration to exclude air from the oesophagus. The sphincter pressure falls to <10 mmHg during deep sleep, and relaxes when a bolus is propelled by the pharyngeal constrictor muscles towards the oesophagus, during vomiting and while belching[6,7] Slow or focal distension, particularly in the proximal oesophagus, favours reflex upper oesophageal sphincter contraction[8]. Unlike the lower oesophageal sphincter there are no significant changes in upper sphincter pressure postprandially or during episodes of spontaneous gastro-oesophageal reflux[6]. In humans the nerve supply of the upper oesophageal sphincter is parasympathetic from the vagi, probably via the pharyngeal plexus The reflex responses to oesophageal stimuli are probably mediated by thoracic and cervical vagal afferents. Cervical vagal cooling in the dog blocks upper oesophageal sphincter contractile response elicited by oesophageal distension with fluid[9]. Efferent nerves to the upper sphincter have their cell bodies in both the dorsal motor nucleus and nucleus ambiguous of the medulla[10].

There are many disorders that affect the swallowing process, but there are few primary motor disorders of the upper oesophageal sphincter Primary motor disorders of upper sphincter function include both abnormalities of the resting tone and abnormalities of cricopharyngeal relaxation and opening.

In its normal contracted state the sphincter can be recognized radiologically as a posterior indentation at the pharyngo-oesophageal junction[11] Seaman, however, regarded this posterior bar as evidence of abnormal muscular spasm[12] Upper oesophageal spasm may occur as an isolated phenomenon and may give rise to the globus syndrome, in which there is a sensation of something sticking in the pharynx although no food has been ingested[13]. In such patients resting sphincter pressures of 140–200 mmHg have been recorded in contrast to pressures of 70–140 mmHg in corresponding normal subjects[13]. Diagnostic criteria remain to be identified for primary cricopharyngeal spasm. Hunt *et al.* reported higher than normal upper sphincter pressures in patients with reflux oesophagitis[14] and Belsey noted an improvement in these patients' symptoms after antireflux surgery[15]. This association between gastro-oesophageal reflux and cricopharyngeal spasm is controversial, but emphasizes the need to rule out reflux before a diagnosis of primary upper sphincter spasm can be made. Experimentally, Freiman *et al.* demonstrated an increase in upper sphincter pressure in response to intraoesophageal acid in a canine model[9] The maximum response to acid occurred on perfusion at the sphincter and the response was less as acid was perfused more distally. Clinically, Gerhardt *et al.* demonstrated a similar response to acid perfusion in humans[8]. However, Kahrilas *et al* studied the effect of spontaneous gastro-oesophageal reflux on upper sphincter pressure and were unable to detect any change in pressure using a superior manometric technique which employed a sleeve sensor[6]. In patients with pathological gastro-oesophageal reflux reports are also conflicting[14,16].

Primary abnormalities of cricopharyngeal relaxation and opening involve either incomplete relaxation or premature closing of the sphincter. Although incomplete relaxation of the upper sphincter can be secondary to underlying diseases such as polio, recurrent laryngeal nerve and bulbar paralysis, and thyrotoxic myopathy, and may occur after partial pharyngectomy, in the majority of instances there is no obvious underlying cause. The term achalasia of the cricopharyngeus

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muscle has been used to describe incomplete relaxation of the sphincter[17]. The diagnosis is suggested by the patient's history and by observing his attempt to drink, and is confirmed by cineradiography[18]. Hypopharyngoscopy and oesophagoscopy are required to exclude other disease. Studies of the pressure dynamics within the pharynx have diagnostic value, although this is not required for diagnosis[19]. Treatment of achalasia, whether primary or secondary, calls for cricopharyngeal myotomy. The results are excellent in most patients[19]. If necessary the sphincterotomy can be performed under local anaesthesia[19]. Bougienage of the cricopharyngeus is of little value, except in children[20].

Premature closing of the cricopharyngeus has been associated with Zenker's diverticulum. Although patients with a pharyngeal pouch frequently exhibit a radiological posterior bar, manometric studies demonstrate normal tonic contraction of the upper sphincter and normal relaxation during swallowing[21] In the patients studied by Ellis *et al.*, sphincter pressures were lower than in control subjects and relaxation was complete[21]. However, contraction of the cricopharyngeus was resumed before the completion of swallowing[21]. Similar findings were reported by Lichter[22], and Duranceau *et al.*[23] found a temporal incoordination in four of ten patients. Cricopharyngeal myotomy extending distally into the upper oesophagus and combined with diverticulopexy gives excellent results in patients with a pharyngeal pouch. Alternatives to cricopharyngeal myotomy and diverticulopexy or diverticulectomy are associated with higher recurrence rates. Dohlman and Mattsson have advocated peroral endoscopic diathermy division of the wall between the diverticulum and the oesophagus, but experienced a recurrence rate of 7 per cent[24].

Achalasia

Achalasia of the oesophagus is the most well defined motility disorder encountered by the surgeon The incidence of achalasia is approximately one in 100 000 per year[25], and there is a regional variation in the prevalence which was 13·4 in 100 000 over a 10-year period in Ireland in contrast to 7·1 in Wales, 10·8 in England and 11·2 in Scotland[26] The clinical symptoms of dysphagia, regurgitation and pain may suggest the diagnosis, and the radiological features may be characteristic but manometric studies remain the most reliable means of establishing a diagnosis Infiltration of the lower oesophageal myenteric plexus by a tumour of the cardia can closely resemble achalasia, and is termed pseudoachalasia It is necessary to perform endoscopy in patients with achalasia[27–29] to exclude this possibility. Achalasia is characterized by absence of peristalsis in the smooth muscle of the oesophageal body, incomplete relaxation of the lower oesophageal sphincter in response to swallowing, and a normal or high resting lower oesophageal sphincter pressure. The resting pressure in the oesophagus is higher than normal, possibly owing to stasis of food, fluid and air. This elevation is accentuated during eating[30] and may reach 120 mmHg (authors' observation) A small number of patients exhibit vigorous achalasia, a variation in which non-peristaltic contractions of more normal amplitude are seen[31,32].

Although the cause of achalasia is unknown it is hoped that the recent advances in the understanding of the physiology of the lower oesophagus will provide the answer. The intramural nerve plexus receives preganglionic innervation either directly from the vagus or indirectly via interneurones, and the postganglionic neurones from these plexuses have both excitatory and inhibitory components to the lower oesophageal sphincter. The mediator of the inhibitory neurones is neither adrenergic nor cholinergic, and the excitatory mediator is cholinergic[33]. The inhibitory mediator is probably vasoactive intestinal polypeptide, neuropeptide Y, enkephalin or substance P[34–36]. Both vasoactive intestinal polypeptide and neuropeptide Y coexist in oesophageal neurones and are the most abundant neurotransmitters in the lower oesophagus; they are therefore considered to be the most likely mediators in lower oesophageal sphincter relaxation[37,38]. In achalasia, incomplete or absent lower oesophageal sphincter relaxation in response to swallowing[39] and a paradoxical contractile response to cholecystokinin–octapeptide[40] indicate absent or functionally impaired postganglionic inhibitory neurones. Exaggerated responses to cholinomimetics also suggest denervation. A reduction in the number of ganglion cells in the myenteric plexus in the affected part of the oesophagus has been suggested in the past[41–43] Aggestrup *et al.*[44] have demonstrated a diminished vasoactive intestinal polypeptide nerve supply and a significantly reduced concentration of vasoactive intestinal polypeptide in the oesophageal smooth muscle of patients with achalasia. The most powerful neurotransmitter, identified with 400 times the ability of vasoactive intestinal polypeptide to induce lower oesophageal sphincter relaxation, is calcitonin gene-related peptide, and calcitonin gene-related peptide-immunoreactive nerves have been shown to innervate the lower oesophageal sphincter. Studies in achalasia patients are awaited[45] It is still uncertain, however, whether the degenerative changes in the intramural neurone in patients with achalasia are a consequence or a cause of the disease[41,46]. Recent observations argue against a general neuronal degeneration in achalasia, as the cholinergic innervation of the lower oesophageal sphincter in achalasia is either normal or only minimally impaired[47], and within the non-cholinergic non-adrenergic pathway substance P levels in the lower oesophagus are unaffected in achalasia[48].

These changes in the innervation of the oesophagus in achalasia relate to the postganglionic intramural plexuses. There is some inconclusive evidence that a more generalized neurological defect exists. Both structural and functional defects have been shown in the vagus of achalasia patients[41,49–51]. Degenerative changes in both myelinated and non-myelinated vagal nerve fibres are found in surgical resection specimens[41,52]. However, the degree of nerve fibre involvement is highly variable, and the significance of such changes in necropsy material and their relationship to the intramural ganglion cell loss is unclear. Reports that 30–50 per cent of patients with achalasia demonstrate abnormal gastric secretory response to insulin-induced hypoglycaemia have been used as evidence that abnormal vagal function is present in achalasia patients[53–55]. Others suggest that this is due to a reduction in parietal cell mass rather than vagal dysfunction, and have failed to confirm abnormal secretory patterns[54]. The functional status of the vagus nerve supplying both the alimentary tract and heart was completely normal in most of the 28 patients with achalasia studied by Atkinson *et al.*[56]. Abnormalities in the dorsal motor nucleus in humans with achalasia have been reported by Kimura[51], and stereotaxic ablation of the dorsal motor nucleus has produced an achalasia-like disturbance in oesophageal function in both canine and feline models[57].

Apart from the neurological abnormalities present, changes in the smooth muscle itself have been demonstrated[41,52,58,59] The abnormalities are variable and non-specific, and suggest denervation atrophy rather than a primary muscular defect However, it is not clear whether previous forceful dilatation could produce similar changes. At the level of the neuromuscular junction and effector organ the mechanism of lower oesophageal sphincter relaxation involves the cyclic nucleotides cAMP and cGMP with their respective cyclic nucleotide-dependent protein kinases[60,61] Vasoactive intestinal polypeptide and isoproterenol both produce lower oesophageal sphincter relaxation associated with an increase in cAMP content and an activation of cAMP-dependent protein kinase in the opossum[60,61]. These pathways remain to be studied in the oesophageal smooth muscle from patients with achalasia.

In summary, the site or cause of the disorder in achalasia is yet to be determined. Currently available knowledge suggests that further evidence of a selective denervation phenomenon involving the non-cholinergic non-adrenergic inhibitory nerves, which have as their neurotransmitters vasoactive intestinal polypeptide and neuropeptide Y, should be sought. A generalized neurological disorder or smooth muscle defect is unlikely to be present The underlying cause of such denervation is not understood and may be toxic, infectious, degenerative or metabolic in origin.

The treatment of achalasia consists of forceful dilatation or myotomy. There is no convincing evidence that pharmacological therapy has a significant role in management, particularly as dilatation or myotomy produces good or excellent results in 90 per cent of patients. Many reports of successful pharmacological manipulation of the lower oesophageal sphincter and oesophageal body in achalasia have appeared in recent years. Satisfactory response to terbutaline sulphate (a β-adrenergic agonist)[62], aminophylline[62], isosorbide dinitrate[62–65] and nifedipine[64,66–69] has been reported. None of these claims is based on sufficient numbers of patients in prospective or placebo-controlled trials. The only role of these agents at present would seem to be as an adjunct to partially successful dilatation or surgery, or when age or medical status of the patient prevents adequate dilatation or surgery.

It is impossible to state definitively whether forceful dilatation or surgical myotomy is superior in the management of achalasia. Only one prospective randomized trial has been undertaken. Csendes *et al.*[70] reported good or excellent results in all 20 patients treated surgically in contrast to only 12 of 18 (67 per cent) patients treated by dilatation. The mean follow-up was short (3·5 years), the numbers studied small, and the technique of dilatation has been criticized on the grounds of its very short duration (two dilatations of 3–5 s) and the use of atropine, which may relax the sphincter and thus render the stretch less effective.

Collective reviews of retrospective unrandomized reports of results of surgical and forced dilatation yield results similar to those of Csendes' prospective randomized study[70]. In a review of forceful dilatation therapy for achalasia conducted by Vantrappen and Janssens[71] good or excellent results were reported in 71·8 per cent (range 61–94·5 per cent)[72,73] of a total of 1371 patients. Andreollo and Earlam[74] reported excellent or good results following Heller's operation in 89 per cent (range 65·5–100 per cent)[75–78] of 5002 patients in a literature review extending from 1970–1985. Patients who have failed to benefit from forceful dilatation appear to respond well to myotomy.

Both dilatation and myotomy are relatively safe procedures. The overall mortality for Heller's myotomy is 0·2 per cent[74], with slightly higher mortality rates occurring in small series of patients[79–81]. The mortality rate following forceful dilatation in the Mayo clinic series was 0·46 per cent and in the Leuven series was 0·24 per cent[82,83]. Oesophageal leak following myotomy and perforation following forceful dilatation are the most serious causes of early morbidity Overall, oesophageal fistula and empyema occurs in 0·4 per cent of myotomy patients[74], while the incidence of perforation following forceful dilatation is in the region of 2·3 per cent, ranging from 1·1 to 4·9 per cent[84–86]. Vantrappen *et al* [87] report impressive results in managing these perforations conservatively, though most would advocate early surgical repair particularly in view of the element of distal obstruction due to the defective lower sphincter[84,88] The most troublesome late complication following therapy is reflux oesophagitis leading to the formation of late stricture. This is more common following myotomy than forceful dilatation. The true incidence of reflux oesophagitis after myotomy is not clear; Ellis *et al.*[89] and Okike *et al.*[82] report a 3 per cent incidence of clinically significant reflux oesophagitis. Other reports claim a 20–50 per cent incidence of gastro-oesophageal reflux after myotomy[75,90–92].

Such diverse reports reflect the various methods employed in assessing gastro-oesophageal reflux and the significance attached to reflux when detected. The overall incidence in Andreollo and Earlam's review was (mean(s.d)) 8·6(7·0) per cent[74]. Vantrappen and Hellemans[83], in a review of 1045 cases collected from 16 published papers on achalasia treated with pneumatic dilatation, found a 10 per cent incidence of reflux oesophagitis. The incidence of peptic stricture accurately reflects the significance of gastro-oesophageal reflux following treatment. Results from the Mayo clinic from Ellis[93], and Okike[82], show a 3 per cent incidence of peptic stricture following myotomy. Vantrappen reported a 0·7 per cent personal incidence of peptic stricture following pneumatic dilatation[71], and found a 3·4 per cent incidence in a literature review[83].

It may be reasonable to accept forceful dilatation as the initial treatment, particularly in patients over 45 years of age, with a history of >5 years and with a moderately distended oesophagus[71,94]. Dilatation should not be performed more than twice, particularly in young patients. Patients who do not respond to two dilatations are unlikely to benefit from further dilatations. The risk of perforation increases as the number of dilatations increases. Multiple dilatations make the operation of myotomy technically more difficult owing to obliteration of tissue planes and fibrous adhesions. Future reports on forceful dilatation should take account of the variety of dilators and techniques employed in order to be clinically useful. Assessment of balloon size, single *versus* multiple dilatations and duration of distension are also needed.

When performing oesophageal myotomy for achalasia we prefer a left thoracotomy approach, extending the myotomy from the inferior pulmonary vein to the gastro-oesophageal junction[95]. It is important to avoid extending the myotomy on to the anterior gastric wall. Extension of the myotomy to only 0·5 cm distal to the gastro-oesophageal junction is adequate to relieve symptoms but will still prevent gastro-oesophageal reflux. This epithelial junction can be seen when the mucosa has been mobilized and is the only accurate way of limiting the distal incision. Intraoperative manometry as an adjunct to surgery has been suggested by Hill *et al.*[96]. The incidence of gastro-oesophageal reflux following this approach is 7·7 per cent. Addition of an antireflux procedure results in a 7·3 per cent incidence of gastro-oesophageal reflux, a difference which is not significant[74]. On the other hand if a transabdominal approach is used when performing the myotomy the incidence of gastro-oesophageal reflux is 13·2 per cent. The incidence is reduced to 7·4 per cent by adding an antireflux procedure[74] and this may be the only indication for the combination of myotomy and an antireflux procedure

When symptoms recur owing to incomplete myotomy or healing of the myotomy incision, good results can be obtained by remyotomy[97–100]. Resection is indicated when recurrent symptoms occur in the presence of gross dilatation[99]. Demos[100], on the other hand, recommends performing a Y–V cardioplasty in patients with true megaoesophagus with areas of kinking. In addition he recommends a cardioplasty when recurrent symptomatic achalasia has occurred in the presence of an apparently complete myotomy.

There is a sevenfold increased incidence of squamous cell carcinoma of the oesophagus in patients with long-standing untreated achalasia. Harley[101] reviewed 3679 cases of achalasia and found an incidence of carcinoma of the oesophagus in achalasia patients of 3·3 per cent with a range of 0·3–20 per cent This incidence may not change even after seemingly successful surgical management[102]. The cause of this is unknown but may be due to the chronic retention of oesophageal content which has been shown to have a pH between 4 and 5·5 and a high lactic acid content[103]. These tumours may arise anywhere in the oesophagus and, because of the confusion caused by the symptoms of achalasia may remain undiagnosed until late, with a consequently worsened prognosis

Diffuse oesophageal spasm

Diffuse oesophageal spasm is a rare disorder of oesophageal motility. Unfortunately, the classification of those motility disorders previously referred to as oesophageal spasm has evolved in an ill-defined manner, and today many of the patients previously felt to have had diffuse oesophageal spasm would certainly be reclassified. This makes interpretation of published reports difficult. The one diagnostic group to emerge clearly from the confusion consists of patients with nutcracker oesophagus.

Characteristically, patients with diffuse oesophageal spasm present with central chest pain and/or dysphagia[104]. The pain may have many features in common with angina pectoris associated with myocardial ischaemia[105]. Often the patients are referred to the gastroenterologist or surgeon by a cardiologist after full investigation has failed to reveal underlying obstructive coronary artery disease. The initial symptom response often seen with nitroglycerine is probably caused by the smooth muscle relaxant effect of the drug on the oesophageal muscle[106–108].

The diagnosis of diffuse oesophageal spasm is based on manometric findings of simultaneous contractions in response to wet swallows in the presence of normal lower oesophageal sphincter function[109–111]. These simultaneous contractions are not present in all swallows, but should be present in ≥30 per cent. Usually the contractions are multi-peaked (≥3 peaks), and prolonged (≥7·5 s). The amplitude of these waves is not of diagnostic significance, and may be low, normal or high[99,102]. When the waves are almost all simultaneous it may be difficult to differentiate between diffuse oesophageal spasm and vigorous achalasia in which the wave amplitude is relatively normal[32]. The inability of the sphincter to relax in the latter is the main differentiating feature. There are anecdotal reports of intermediate forms of dysmotility However, many are poorly documented without full details of investigations. Other investigations of oesophageal function will usually help to establish the true diagnosis. This is particularly true of the barium swallow In diffuse oesophageal spasm the appearance may vary from a mild serration of the margins of the barium-filled oesophagus (tertiary contractions) to subdivision or outpouching of the oesophageal outline. The striking radiographic findings that may be associated with this condition have prompted the use of colourful synonyms, including curling, beading, corkscrew oesophagus, rosary bead oesophagus, functional diverticula, pseudodiverticulosis, segmental spasm, elevator oesophagus and knuckle-buster[112]. These features are very non-specific and are frequently seen in elderly patients with presbyoesophagus[113,114]. The barium swallow is of use only as an adjunct to establish the diagnosis when difficulty is experienced in distinguishing between diffuse oesophageal spasm and achalasia

To increase diagnostic accuracy, a number of provocation tests have been suggested. The cholinergic agents metacholine, bethanechol, carbachol, the cholinesterase inhibitor edrophonium chloride, along with pentagastrin and ergonovine maleate have all been used[115–121]. In the absence of a complete cardiac evaluation it is unwise to use ergonovine. Edrophonium is without this risk and is the most widely employed provocation test agent. A negative response does not exclude the disease Typical manometric features may be provoked in the absence of symptoms, and symptoms may also be provoked in patients with achalasia and nutcracker oesophagus. The diagnostic value of provocation tests is, therefore, somewhat limited

There is no consensus of opinion regarding the relationship between the manometric findings of diffuse oesophageal spasm and the symptoms that the patient experiences A patient with periodic chest pain and/or dysphagia will exhibit manometric abnormalities while asymptomatic, and even when symptoms are reproduced using provocation tests such as ergometrine there is no correlation between the symptoms and worsening of the manometric findings[115,119,122,123]. Furthermore, completely asymptomatic elderly volunteers exhibit features typical of diffuse oesophageal spasm on manometry[113,114]. Other studies of oesophageal function do not correlate with the degree of abnormality demonstrated on manometry in patients with diffuse oesophageal spasm Clouse and Lustman demonstrated an association between diffuse oesophageal spasm and psychiatric illness such as depression and anxiety[124].

For diffuse oesophageal spasm to be considered a primary disorder of oesophageal motility a complete investigation of the oesophagus must be undertaken to exclude coexisting disorders. Manometric criteria alone are insufficient to establish the diagnosis.

Diffuse oesophageal spasm cannot, therefore, be diagnosed when there is coexisting gastro-oesophageal reflux; an organic lesion of the oesophagus such as carcinoma, stricture, web or diverticulum; previous oesophageal surgery such as vagotomy or antireflux surgery; and systemic disorders known to influence oesophageal motility such as diabetes mellitus, chronic alcohol abuse and scleroderma. Similar reservations apply to nutcracker oesophagus Before making a diagnosis of diffuse oesophageal spasm on the basis of manometric criteria all patients should undergo upper gastrointestinal endoscopy and 24-h ambulatory pH monitoring to demonstrate that coexisting pathology is not present.

McCallum described a clinical, radiological and manometric syndrome identical to diffuse oesophageal spasm and secondary to gastro-oesophageal reflux[125]. Little *et al.* described the production of simultaneous repetitive contractions in the oesophageal body in a feline model of incomplete obstruction of the lower oesophagus[126]. Similar findings were present in patients with benign peptic oesophageal strictures and patients with excessively tight antireflux surgery. Indeed, this response of the oesophageal body to distal obstruction has previously been suggested to be relevant in diffuse oesophageal spasm, and some cases of diffuse oesophageal spasm with incomplete relaxation of the lower oesophageal sphincter have been reported[127]. The facts that the great majority of patients with diffuse oesophageal spasm have normal lower oesophageal sphincter relaxation and that oesophageal transit time is normal in many cases of diffuse oesophageal spasm[127,128] argue against this being caused by abnormal lower oesophageal sphincter function. This further emphasizes the need for full investigation of the oesophagus and the need for awareness of the underlying disorders which can cause abnormal motor patterns that mimic diffuse oesophageal spasm.

Although the underlying cause of diffuse oesophageal spasm is unknown there is some evidence that the abnormal contractions could result from a neuropathic disorder. The possibility of a common pathophysiological mechanism between diffuse oesophageal spasm and achalasia has been entertained[129]. The main feature in common is the exaggerated response to cholinomimetics, suggesting a denervation phenomenon[116,130]. The controversy surrounding the finding of incomplete lower oesophageal sphincter relaxation in a proportion of patients with diffuse oesophageal spasm has also been used as evidence for a common aetiology with achalasia[116]. It is unlikely, however, that a distinct lesion primarily involving the lower oesophageal sphincter could be operative, and a more diffuse lesion seems probable since abnormal contraction waves are always observed, yet failed lower oesophageal sphincter relaxation is noted in few cases. Recent electromyographic studies have demonstrated spike-independent contractions of the oesophageal body in patients with diffuse oesophageal spasm[131]. These findings may represent impaired inhibitory neural mechanisms. Heightened excitability of spontaneous spike activity has also been reported in patients with diffuse oesophageal spasm, an observation similarly made in patients with achalasia. This finding was also considered to represent impaired non-cholinergic, non-adrenergic inhibitory neurones[132]. An imbalance between excitatory and inhibitory innervation could conceivably lead to simultaneous and repetitive contractions, possibly of increased amplitude[133]. Despite these data suggesting functional derangements of the neural control of muscle contraction in patients with diffuse oesophageal spasm, there is little documentation of a neuropathological lesion. Disrupted vagal fibres within the oesophageal wall have been noted by electron microscopy in a small group of patients with diffuse oesophageal spasm[134]. Whether this finding applies to all patients with similar manometric findings is unclear. The only finding present in the majority of patients with diffuse oesophageal spasm is hypertrophy of the smooth muscle in the oesophageal wall, which can be demonstrated on barium swallow[135], computed tomography[136] or at the time of operation[137,138].

Because of the diagnostic confusion, the poorly understood pathophysiology, the inability to link symptoms to manometric abnormality, and the association with psychiatric disorders, the treatment of diffuse oesophageal spasm remains uncertain. A detailed history is necessary to establish symptom frequency and severity. Any precipitating cause should be eliminated as far as possible. Some patients respond to reassurance that the pain is not of cardiac but of oesophageal origin, that it will not progress and is not life-threatening. Short-acting and long-acting nitrate preparations[27–29,139] as well as hydralazine[140] have, in uncontrolled trials, relieved symptoms and improved manometric or radiographic findings in some patients. When systematically studied, the effects of these agents on manometric parameters in the oesophageal body may be minimal[141,142] The calcium antagonists, because of their actions on smooth muscle, have been reported to be of benefit. However, most reports are uncontrolled and anecdotal[143–146]. When a placebo control was employed, nifedipine was no better in the management of chest pain despite its significant effects on motility[147]. In view of the poor and unreproducible nature of the effects of these agents and the high incidence of psychiatric disorders, Clouse *et al*. studied the role of antidepressant therapy in patients with oesophageal contraction abnormalities[148]. As with their previous study[124], they did not separate diffuse oesophageal spasm patients from others with less classical abnormalities on manometry. They chose to study trazodone hydrochloride because it has no known effect on oesophageal motility. Patients receiving trazodone hydrochloride reported a significantly greater improvement than those receiving placebo. The response was varied, and both treatment and placebo groups had a high response rate. As with other studies, response was not associated with manometric changes on repeat testing

When symptoms are frequent, severe and do not respond to reassurance and/or medical management, myotomy may be necessary. The surgical management of diffuse oesophageal spasm is controversial. Because of the rarity of the disease, there are only three series reported of more than 15 patients[149–151], and only one with 5-year follow-up[151]. Of 149 cases reported, excellent results were obtained in 67 per cent (range 48·5–85·7 per cent)[138,149–155]. No specific criteria for selecting patients for surgery are suggested. The main areas of controversy centre on the extent of myotomy employed and the necessity of adding a hernia repair. Henderson *et al.* argue that the myotomy should be performed through the left chest and that it should extend from the proximal stomach to the apex of the chest[151]. Their reason for the left approach is to facilitate a total fundoplication hernia repair. The choice of myotomy extending to the apex of the chest is supported by autopsy studies, which demonstrate that smooth muscle is predominant over striated muscle up to the lower half of the upper oesophagus[151]. Unfortunately in Henderson's most recent report insufficient detail is given of the preoperative manometric findings, and one of his patients had ulcerative oesophagitis and two had an oesophageal stricture. Ellis *et al.* on the other hand argue for preservation of the lower oesophageal sphincter and limiting the extension of the myotomy to the distal two-thirds of the oesophagus[149].

Nutcracker oesophagus

Also known as symptomatic oesophageal peristalsis, the nutcracker oesophagus represents the most common oesophageal motility disorder. The proportion of patients with nutcracker oesophagus has increased as more patients with angina-like chest pain of non-cardiac origin are investigated for oesophageal disease. Nutcracker oesophagus accounts for 28–45 per cent of motor disorders in patients with non-cardiac angina-like chest pain[112,156–158].

Typically patients with nutcracker oesophagus present with central chest pain which may radiate to the epigastrium, into the neck or down the left arm[159]. Often the patients relate symptoms to exertion, hence their referral to the cardiologist[160]. Although dysphagia may be present[120,161] it is not as frequent as in diffuse oesophageal spasm (50–70 *versus* 100 per cent)[151]. It has been suggested that nitrates may be of benefit, particularly during an episode of pain, and this leads to further diagnostic difficulty since the cardiologist usually interprets this as further evidence of underlying ischaemic heart disease.

Nutcracker oesophagus is defined as the presence of high amplitude peristaltic waves in the distal oesophagus in a patient with symptoms of chest pain and/or dysphagia[162–164] The presence of normal peristalsis separates this disorder from classic diffuse oesophageal spasm. The peristaltic waves are usually prolonged and may be multi-peaked, though more often they are single-peaked[165]. To make a diagnosis of nutcracker oesophagus a full evaluation of the oesophagus must be undertaken to exclude coexisting pathology. When the manometric profile of nutcracker oesophagus is found in association with other oesophageal pathology such as reflux oesophagitis or stricture we should not make the diagnosis. The diagnostic criteria of nutcracker oesophagus vary in different institutions. The original description of this disorder required a mean peristaltic wave amplitude of > 120 mmHg, averaged over ten wet swallows in the distal 5 cm of the oesophagus[121,156,162]. Traube *et al*[166] required a value > 140 mmHg, and in a recent report Ott *et al.*[167] required a value > 180 mmHg. The mean(s.d.) normal distal amplitude in Ott's study, derived from a group of 95 healthy subjects, is 100(80) mmHg. Gelfand and Botoman consider a mean amplitude of ± 150 mmHg as diagnostic[168]. These variations arise from differences in normal populations rather than differences in manometric technique. At present we consider a mean amplitude of the peristaltic wave ⩾ 150 mmHg in the lower 5 cm of the oesophagus as diagnostic of nutcracker oesophagus. Drane *et al.* attempted to correlate manometric findings with evidence of poor bolus clearance from the distal oesophagus[169]. In patients with mean peristaltic amplitudes between 120 and 150 mmHg, only 50 per cent had evidence of delayed transit using radionuclide oesophageal scintigraphy, while 81 per cent of those with amplitudes ⩾ 150 mmHg had abnormal radionuclide oesophageal scintigraphy. Agreement between the two techniques was far from good

These and the results of other radionuclide oesophageal scintigraphy studies[170,171] suggest that the functional disorder of nutcracker oesophagus has a pathological basis. However, variability in the manometric results in nutcracker oesophagus is a significant problem. Spurling *et al.* found a high variability in manometric results when patients were studied on multiple occasions over a 1-month period[172]. Drane *et al.* reported that 31 per cent of patients on repeat examination were classified as normal[169], and Johnson *et al.* reported normal manometry in three of 11 patients on longer follow-up[173] As in diffuse oesophageal spasm, there is often a lack of temporal correlation between symptoms and manometric abnormalities, even when the symptoms are reproduced during provocation tests[119,174]. Abnormal waves are seen during asymptomatic periods and alteration of the manometric profile during symptoms is often absent[174] Furthermore, relief of chest pain, the hallmark of the disease, does not coincide with the reduction in the amplitude of the oesophageal contractions[148]. Although patients frequently relate symptoms to effort, we have demonstrated that the amplitude of peristaltic contractions in patients with nutcracker oesophagus during exercise is, paradoxically, within normal limits[175]. These findings indicate that the relationship of chest pain and high-amplitude oesophageal peristaltic waves is not a causal one.

Richter and colleagues, using balloon distension to study the mechanism of oesophageal pain, found that non-cardiac chest pain was related to lower pain thresholds, a mechanism independent of oesophageal contractions, wall tone or wall resistance[176,177]. Support for this abnormal perception of distension comes from Edwards in a report entitled 'The tender oesophagus'[178], and Vantrappen *et al.* who describe the condition as the irritable oesophagus[179]. There are striking similarities between nutcracker oesophagus and the irritable bowel syndrome. Patients with irritable bowel syndrome experience lower abdominal pain with rectal balloon volumes not generally perceived by normal subjects[180,181] or anxious patients without bowel symptoms[182]. No evidence of abnormal muscular activity or increased gut wall tension was found in these studies. The pathogenesis of the lower visceral pain threshold in patients with nutcracker oesophagus and irritable bowel syndrome is poorly understood. In three separate investigations the prevalence of subjects with psychiatric illness ranged from 70 to 92 per cent in patients with the irritable bowel syndrome but was only 18 per cent in medically ill controls[183–185]. A preliminary report comparing a small group of patients having nutcracker oesophagus with patients who had irritable bowel syndrome and asymptomatic subjects suggested similarities between the two symptomatic groups[186] This was further supported by a report from Clouse and Lustman, in which psychiatric illness was present in >80 per cent of patients with symptomatic high-amplitude oesophageal contractions, compared with 31 per cent of patients with normal manometric findings[124]. The same diagnoses (depression, anxiety disorder and somatization disorder) were largely responsible for the increased prevalence of psychiatric illness in both nutcracker and irritable bowel syndrome patients[124]. Patients in both groups were predominantly women (2·1). Intense environmental stimuli can provoke tertiary contractions in the oesophageal body, and emotional tension or psychic stress can evoke changes in oesophageal motor activity[187].

It is possible that high-amplitude contractions may be an unassociated marker of this pain syndrome[188]. It is possible that nutcracker oesophagus may not be a marker for oesophageal disease or oesophageal-related pain. It is also possible that the high incidence of psychiatric illness may be the result of, rather than the cause of, a disorder which perplexes not only the patient but also the attending physician. Patients with coronary artery spasm (Prinzmetal's angina) have a high incidence of motor disorders of the oesophagus[189]. A common pathophysiology has been suggested, as both coronary artery spasm and oesophageal contractions are mediated by alpha, histamine and muscarinic receptors[189,190] Ergonovine, which is widely used for diagnostic provocation of coronary artery spasm, is capable of inducing abnormalities in oesophageal contractions. Evans and Lum demonstrated that hyperventilation is an important cause of chest pain in patients with normal coronary arteries[191]. This hyperventilation was capable of inducing impressive electrocardiographic S–T changes. Rasmussen *et al* reported that hyperventilation could aggravate both coronary artery spasm and oesophageal motor activity[189]. Spears and Koch reported 18 patients with mitral valve prolapse, 12 of whom had motor disorders on oesophageal manometry[192]. Sataline recently reported an association between mitral valve prolapse and irritable bowel syndrome[193]. Association between nutcracker oesophagus and biliary dyskinesia has also been reported[194]. For the moment it would seem wise to reserve judgement as to whether the nutcracker oesophagus represents a true primary disorder of oesophageal motility, a reflection of disease distant from the oesophagus, or a new manifestion of the irritable bowel syndrome.

Obviously the treatment of nutcracker oesophagus is somewhat empirical as many reports are anecdotal. The treatment of non-cardiac chest pain of oesophageal origin in general is difficult. Ward *et al.* reported long-term follow-up of symptomatic status of patients with non-cardiac chest pain and specifically addressed the question: Is diagnosis of oesophageal aetiology helpful[195]. They concluded, after a follow-up of mean length 21·8 months, that patients diagnosed as having an oesophageal cause for their non-cardiac chest pain usually continued to have recurrent pain. Furthermore, a specific diagnosis did not increase the likelihood of pain resolution. However, patients who understood that the oesophagus was the source of their pain were significantly less likely to feel disabled by their pain and to require continued evaluation. These findings were independent of any treatment programme. Similar findings have been reported by Burns *et al.*[196]. Suggested treatments include short- and long-acting nitrates[105], calcium antagonists[197,198], antidepressants[148], psychological support and reassurance[148], physiotherapy to restore normal breathing patterns[191], dilatation[199], and even surgical myotomy in refractory cases[200]. Symptomatic improvement with bougienage appears to be mainly a placebo effect, as Winters *et al.* reported improvement when dilated by a dilator of such small diameter as to be a sham dilator[199]. Traube *et al.* advocate long myotomy for refractory cases and report their results in four cases[200]. It is, however, far from clear whether the symptom relief can be attributed to the myotomy, as three of the four cases had evidence of abnormal gastro-oesophageal reflux, no 24-h pH studies were performed, and all three cases underwent simultaneous antireflux surgery. This underlines the importance of excluding associated oesophageal pathology before diagnosing nutcracker oesophagus. Richter and Castell stress that true intractability must be quite rare as they have not felt it necessary to refer a single patient with nutcracker oesophagus for myotomy despite seeing over 100 cases in a 3-year period[201].

Conclusion

Manometry is the best available method for diagnosing the motor disorders of the oesophagus. The criticism that manometric techniques differ widely among institutions has been largely overcome since the introduction of the low-compliance hydraulic method. As a result the comparison of manometric profiles is made possible between institutions. What is now required is a strict adherence to the accepted categories of abnormalities As a result confusion will be less likely. With the advent of a completely ambulatory system for performing manometry it is reasonable to assume that manometry will closely reflect normal events in the oesophagus and allow better correlation between symptoms and abnormal motility, just as ambulatory pH monitoring has revolutionized the understanding of gastro-oesophageal reflux.

Even if a classic abnormal motor pattern is detected on manometry this is insufficient evidence on which to base a diagnosis. All the abnormal manometric profiles can be detected in other situations. The most important examples are pseudoachalasia secondary to tumours of the cardia and motor disturbances associated with gastro-oesophageal reflux. Every form of motor disorder has been described in association with gastro-oesophageal reflux Patients should rarely if ever be diagnosed as having diffuse oesophageal spasm or nutcracker oesophagus when there is evidence of abnormal gastro-oesophageal reflux or complications of reflux such as stricture. Future reports should exclude all cases associated with gastro-oesophageal reflux and include results of pH monitoring Non-specific oesophageal motility disorders is the general term applied to abnormal contraction patterns identified at manometry which do not fit into any recognized category. These aberrant patterns we sometimes find in association with non-cardiac chest pain, but their clinical significance is not understood at present.

The results of myotomy for achalasia of the lower oesophageal sphincter and for upper oesophageal sphincter dysfunction associated with a diverticulum are excellent. The outcome of myotomy for upper sphincter dysfunction without a diverticulum is less certain. Surgery is rarely indicated in diffuse oesophageal spasm; nutcracker oesophagus should be treated conservatively and surgery is never indicated. Advances in the neurophysiology of the oesophagus in these conditions will lead to a better understanding of their possible inter-relationships and clarify the therapeutic options.

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Abdominal pain: a surgical audit of 1190 emergency admissions

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In an audit of 1190 emergency admissions with abdominal pain (1166 patients) in a general surgical unit, the diagnosis was non-specific abdominal pain (NSAP) in 415 (35 per cent), acute appendicitis in 200 (17 per cent) and intestinal obstruction in 176 (15 per cent). The largest number of admissions occurred in the age groups 10–29 years (31 per cent) and 60–79 years (29 per cent). Surgical operations were performed in 551 patients (47 per cent) and there was a 16 per cent incidence of unnecessary appendicectomy (22 per cent in the age group 20–29 years). Fifty-one deaths resulted in a 30-day hospital mortality rate of 4·4 per cent and a perioperative mortality rate of 8 per cent. The mortality rate increased significantly in patients aged $\geqslant 60$ years, and patients aged 80–89 years had a perioperative mortality rate of 20 per cent. The causes of perioperative death included laparotomy for inoperable disease (28 per cent), ruptured abdominal aortic aneurysm (23 per cent), perforated peptic ulcer (16 per cent) and colonic resections (14 per cent). The perioperative mortality rates for ruptured aneurysm and perforated ulcer were 71 and 23 per cent respectively. The duration of inpatient stay increased significantly with the age of the patients, including those with NSAP. The results of the study indicate a need to review the methods of management of ruptured aortic aneurysm and perforated peptic ulcer, the methods of diagnosis of appendicitis, particularly in young females, and the factors that determine the duration of stay of patients suffering from NSAP.

Keywords: Acute abdomen, abdominal pain

The majority of emergency admissions to surgical wards are patients complaining of abdominal pain. Surprisingly, there is comparatively little information regarding the clinical spectrum of disease in these patients and the outcome after admission to hospital. Most studies of the acute abdomen have been confined to patients in specific age groups[1–3], to patients with specific diseases[4–7] or particular types of acute presentation[8,9], or to patients who fail to survive a surgical operation[10]. The Confidential Enquiry into Perioperative Deaths (CEPOD)[10] included deaths after urgent or emergency abdominal operations for a range of acute disorders but the study provided no information regarding the relative risks attached to the various disorders which present as an acute abdomen.

For the last 4 years an audit of emergency admissions of patients with abdominal pain in one surgical unit has been carried out; this was to determine the clinical spectrum of disease, the outcome of treatment or investigation, and the implications for bed occupancy.

Patients and methods

The study included all emergency admissions of patients complaining of abdominal pain in one surgical unit of a district general hospital during the period from January 1984 to December 1987. The unit has 30 adult general surgical beds and access to a small number of emergency beds within a paediatric ward. The predominant interest of the unit is gastrointestinal surgery, and the medical staff include one consultant surgeon, one rotation registrar or senior registrar, one senior house officer, and one preregistration house surgeon. The district general hospital serves a population of 302 400[11], and the surgical unit has a 1 day in 5 commitment to admit all surgical emergencies arising within the district during a 24-h period, including vascular and urological cases.

Method of audit

A standard form of discharge summary was used for all admissions including details of the mode of clinical presentation, the results of investigations, the methods of treatment, the operating surgeons, the clinical outcome, and the final clinical diagnosis. A diagnosis of 'non-specific abdominal pain' (NSAP)[8] was recorded when no cause for the abdominal pain was found. The clinical details were transferred to a study proforma for analysis. The dictation of discharge summaries and completion and analysis of the proforma occupied approximately 300 man-hours.

Statistical analysis

The χ^2 test, Fisher's exact test, and the t test for unpaired data were used in the analysis of different variables.

Results

Admissions

During the 4-year period 1166 patients were admitted with abdominal pain. Twenty-three patients were admitted more than once (one patient was admitted on three occasions) resulting in a total of 1190 admissions. There were 579 male patients and 587 female patients of mean age 46 years (range, from 2 months to 98 years), and the peak age groups for emergency admission were 10–29 years (31 per cent of patients) and 60–79 years (29 per cent of patients). There was no significant difference in the rates of admission through different months of the year although there was a slightly increased rate in August due to an influx of visitors in the Exeter area

Clinical diagnosis

The final clinical diagnoses in the 1190 admissions are shown in *Table 1*. The most common diagnoses were non-specific abdominal pain (NSAP), acute appendicitis, and intestinal obstruction; but there were significant differences in the incidence of the presenting illnesses in patients aged <60 years and those aged $\geqslant 60$ years. Intestinal obstruction was the most frequent diagnosis in patients aged $\geqslant 60$ years (28·0 per cent of admissions), followed by NSAP (22·5 per cent), complications of cholelithiasis (8·9 per cent) and colonic diverticular disease

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Table 1 *Diagnoses in 1190 admissions for abdominal pain, and in patients aged <60 years and ≥60 years*

	No. of admissions			
Diagnosis	Total (n=1190)	Age ≥60 years (n=471)	Age <60 years (n=719)	P*
Non-specific abdominal pain	415 (34·9)	106 (22·5)	309 (43·0)	<0·001
Acute appendicitis	200 (16·8)	20 (4·2)	180 (25·0)	<0·001
Intestinal obstruction	176 (14·8)	132 (28·0)	44 (6·1)	<0·001
Urological	70 (5·9)	15 (3·2)	55 (7·6)	<0·01
Cholelithiasis	61 (5·1)	42 (8·9)	19 (2·6)	<0·001
Colonic diverticular disease	46 (3·9)	40 (8·5)	6 (0·8)	<0·001
Abdominal trauma	37 (3·1)	2 (0·4)	35 (4·9)	<0.001
Abdominal malignancy	36 (3·0)	26 (5·5)	10 (1·4)	<0·001
Perforated peptic ulcer	30 (2·5)	20 (4·2)	10 (1·4)	<0·01
Pancreatitis	29 (2·4)	18 (3·8)	11 (1·5)	<0·02
Exacerbated peptic ulcer	17 (1·4)	9 (1·9)	8 (1·1)	n.s.
Ruptured aortic aneurysm	15 (1·3)	14 (3·0)	1 (0·1)	<0·001
Gynaecological	13 (1.1)	1 (0·2)	12 (1·7)	0·002
Inflammatory bowel disease	10 (0·8)	5 (1·1)	5 (0·7)	n.s.
Medical (pneumonia, pulmonary embolism, myocardial infarction, etc.)	10 (0·8)	5 (1·1)	5 (0·7)	n.s.
Mesenteric vascular occlusion	7 (0·6)	7 (1·5)	0	0·003
Gastroenteritis	4 (0·3)	0	4 (0·6)	n.s.
Miscellaneous	14 (1·2)	9 (1·9)	5 (0·7)	n.s

Values in parentheses are percentages, *statistical significance of differences between admissions aged ≥ 60 years and those aged <60 years (χ^2 and exact probability tests), n.s., not significant

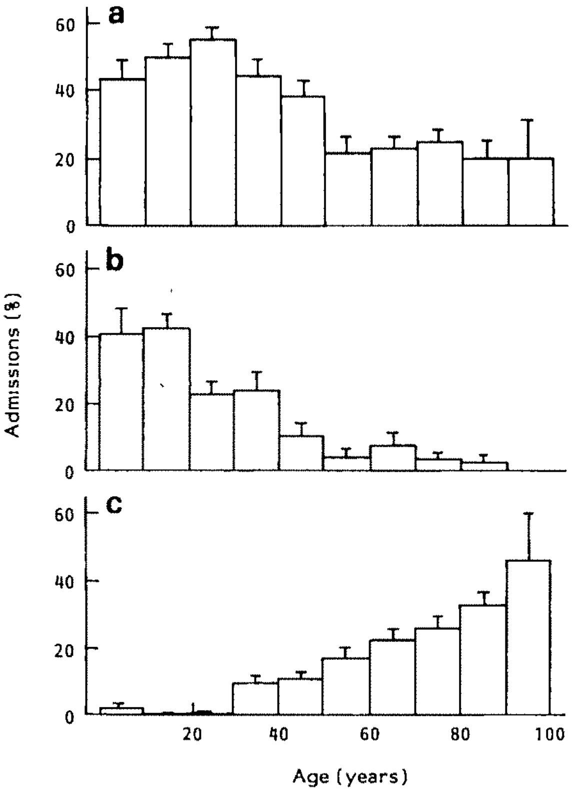

Figure 1 *Age distribution of admissions for* **a** *non-specific abdominal pain,* **b** *acute appendicitis and* **c** *intestinal obstruction (percentages + 95 per cent confidence intervals)*

(8·5 per cent), and acute presentation of various types of abdominal malignancy (5·5 per cent). NSAP (43·0 per cent) and appendicitis (25·0 per cent) were the most frequent diagnoses in patients aged <60 years. The age distribution of the admissions with NSAP, appendicitis, and intestinal obstruction is shown in *Figure 1* and it is apparent that the peak for admissions in the 10–29 age range is due to the large numbers of cases of NSAP (50·8 per cent of admissions) and appendicitis (33·0 per cent of admissions).

The causes of intestinal obstruction are shown in *Table 2*.

Table 2 *Causes of intestinal obstruction*

Cause	No of admissions (n=176)
External hernia	51 (29·0)
Adhesions	37 (21·0)
Carcinomatosis	35 (19·9)
Colonic carcinoma	34 (19·3)
Colonic diverticular disease	4 (2·3)
Volvulus (sigmoid/caecal)	4 (2·3)
Crohn's disease	3 (1·7)
Pseudo-obstruction	3 (1·7)
Miscellaneous*	5 (2·8)

Values in parentheses are percentages; * cause uncertain (no operation) in 3, gallstone ileus in 1 and cystic fibrosis in 1

Interestingly, large bowel obstruction due to colonic carcinoma (19·3 per cent of admissions) was slightly less common than small bowel obstruction caused by external hernia, adhesions, and abdominal carcinomatosis.

Surgical operations

Five hundred and fifty-one of the patients (47·3 per cent) underwent a surgical operation. Using the CEPOD classification[10], 26 (4·7 per cent) were emergency operations (immediate, potentially life-saving procedures, e.g. for ruptured aortic aneurysm and abdominal trauma), 467 (84·8 per cent) were urgent operations (operation performed after adequate resuscitation or preparation, e.g. operations for intestinal obstruction or peritonitis), and 58 (10·5 per cent) were scheduled operations (operation performed as an elective procedure on a scheduled list, e.g. operations for complications of cholelithiasis or recurrent small bowel obstruction). Scheduled operations were more common in older patients (15·8 per cent of operations in patients aged ≥60 years, $\chi^2 = 12{\cdot}49$, $P < 0{\cdot}001$), mainly owing to an increased incidence of complications of cholelithiasis and acute presentation of gastrointestinal malignancies

The most common operations were appendicectomy (35·6 per cent), operations for strangulated external hernia and other causes of small bowel obstruction (22·1 per cent), colonic resections (12·3 per cent), and urgent or scheduled operations for cholelithiasis (5·6 per cent). The incidence of unnecessary appendicectomy in different age groups was related to the age incidence of NSAP. In total, 15·5 per cent of appendices

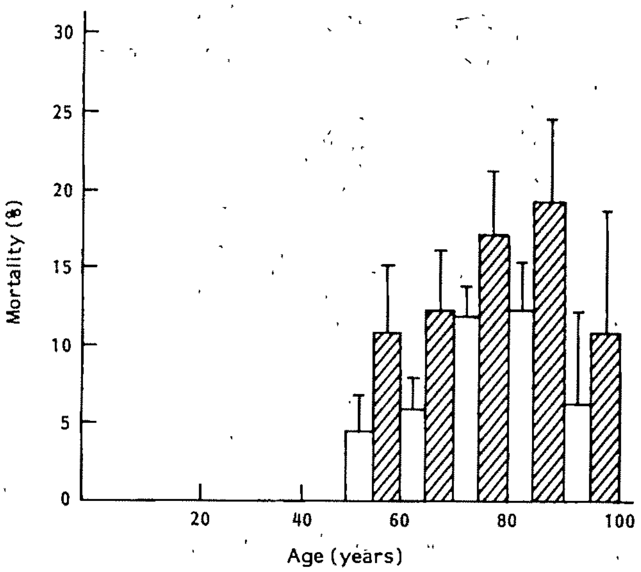

Figure 2 *Age distribution of hospital (☐) and perioperative (■) mortality (percentages and 95 per cent confidence intervals)*

removed proved to be normal and there was a 22·4 per cent incidence in patients aged 20–29 years. Moreover, the error predominantly occurred in female subjects: 77 per cent of patients aged <30 years undergoing an unnecessary appendicectomy were female. Three hundred and twenty operations (58·1 per cent) were performed by a registrar or senior registrar (with or without consultant supervision), 122 (22·1 per cent) were performed by the senior house officer (usually an appendicectomy), and 109 (19·8 per cent) were performed by the consultant.

Mortality

Fifty-one patients died in hospital, resulting in a 30-day hospital mortality rate of 4·4 per cent and a perioperative mortality rate of 7·8 per cent. The mortality rates were age-related (*Figure 2*): the perioperative mortality rate was 12·3 per cent in patients aged 60–69 years, 17·4 per cent in patients aged 70–79 years, and 19·7 per cent in patients aged 80–89 years. The hospital and perioperative mortality rates for patients aged <60 years were 0·7 per cent and 1·6 per cent respectively.

There were eight non-operative deaths. Two patients died during conservative treatment of subacute small bowel obstruction caused by adhesions: one patient (aged 78 years) inhaled gastric contents, and the other patient (aged 60 years) suffered a myocardial infarction. Two patients, aged 72 years and 77 years, died from acute necrotizing pancreatitis, one also suffering a cerebrovascular accident. One patient aged 78 years died from a massive pulmonary embolism, and another aged 82 years died from irreversible congestive cardiac failure. Both patients presented as abdominal emergencies and the absence of abdominal pathology was confirmed at autopsy. Two patients, aged 72 years and 80 years, who were admitted with established incurable malignant disease, died in hospital, in one case as a consequence of the malignancy and in the second case due to a ruptured abdominal aortic aneurysm.

There were 43 perioperative deaths, and in 25 cases (58 per cent) the patient was aged >75 years. The surgical operations were performed by the consultant in ten cases (23 per cent) and by the senior registrar or registrar in 33 cases (77 per cent). The types of surgery resulting in the 43 deaths are listed in *Table 3*. The highest proportion of the deaths (28 per cent) occurred in patients found to have inoperable diseases (massive intestinal infarction or carcinomatosis), closely followed by ruptured aortic aneurysm (23 per cent of deaths). Operations for perforated peptic ulcer and urgent colonic resections accounted for 16 and 14 per cent of deaths respectively. There were no deaths after operations for cholelithiasis or appendicectomy but one patient (aged 77 years) died from a myocardial infarction during an unnecessary laparotomy for suspected ruptured aortic aneurysm.

The perioperative mortality rate for ruptured aortic aneurysm was 71 per cent. The operations were performed by the consultant in six cases and by a senior registrar in four cases. Three of the ten deaths resulted from exsanguination or cardiac arrest during the operation, three were related to postoperative haemorrhage and coagulopathy, and four deaths resulted from acute renal failure. Eight of the ten patients were aged >75 years.

The perioperative mortality rate for perforated peptic ulcer was 23 per cent. The seven deaths occurred in patients with pyloroduodenal ulceration, and six of the seven perforations were treated by simple suture; the remaining patient with a very large perforation and coexisting haematemesis and melaena underwent a Pólya gastrectomy. The operations were performed by a registrar or senior registrar in six cases and by the consultant in one case. Five deaths resulted from cardiac or circulatory failure, and two deaths were related to reperforation of the ulcer following simple suture. Five of the seven patients were aged >75 years.

The perioperative mortality rate for urgent colonic resections was 9 per cent. Three deaths occurred in patients with faecal peritonitis resulting from perforated diverticular disease, two deaths occurred after resections of colonic tumours (one obstructing and one perforated), and one death occurred after a sigmoid resection for volvulus. All the operations were performed by a registrar or senior registrar. The causes of death included uncontrolled sepsis and multiple organ failure (four cases with faecal peritonitis), congestive cardiac failure (one case), and pulmonary embolism (one case). All six patients were aged >75 years.

Duration of stay

The 1190 admissions resulted in a total bed occupancy of 8096 inpatient days. Patients aged 70–79 years were the major users of beds (1849 inpatient days) and patients aged $\geqslant 70$ years accounted for 39 per cent of the bed occupancy. The mean duration of stay increased significantly after the age of 40 years ($t=10{\cdot}45$, $P<0{\cdot}001$), and the duration of stay for patients with NSAP was also age-related (*Figure 3*). Patients with NSAP aged $\geqslant 70$ years remained significantly longer in hospital ($t=11{\cdot}53$, $P<0{\cdot}001$) and they were more frequently subjected to definitive inpatient investigations (endoscopy, barium study, ultrasound, etc.): 76 per cent of patients aged $\geqslant 70$ years underwent such investigations compared with 32 per cent of patients aged <70 years ($\chi^2=48{\cdot}06$, $P<0{\cdot}001$).

Discussion

NSAP was the most common diagnosis in emergency admissions (35 per cent of admissions), but there were age-related differences in the incidence of NSAP and the other diagnoses; intestinal obstruction, most frequently due to a strangulated external hernia, was the most common diagnosis

Table 3 *Nature of surgery resulting in 43 perioperative deaths*

Nature of surgery	No. of cases	No. of deaths
Laparotomy and closure (inoperable)*	16	12 (75·0)
Ruptured aortic aneurysm	14	10 (71·4)
Perforated peptic ulcer	30	7 (23·3)
Colonic resection	68	6 (8·8)
Small bowel surgery (external hernia, adhesions, resection, bypass)	122	6 (4·9)
Miscellaneous (gynaecological, renal, trauma, etc.)	34	1 (2·9)
Negative laparotomy	39	1 (2·6)

Values in parentheses are percentages; * carcinomatosis in 11, superior mesenteric vascular occlusion in 5

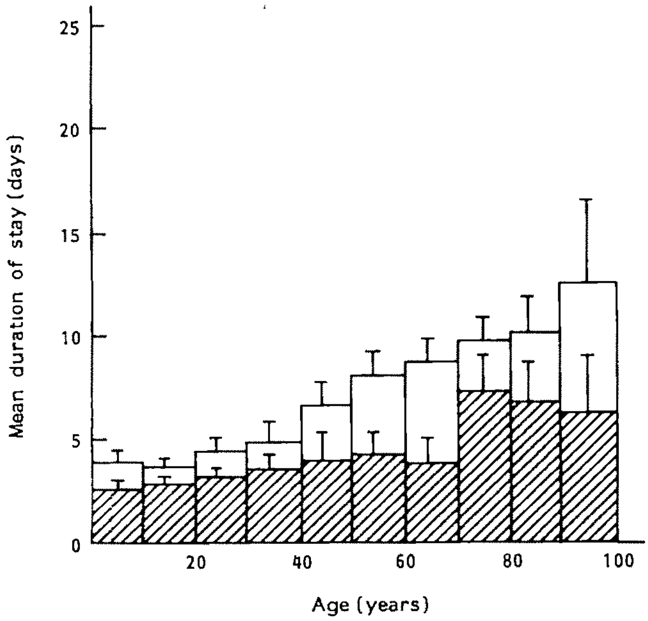

Figure 3 *Mean duration of stay for each age group (all cases (□) and non-specific abdominal pain admissions (■)) and 95 per cent confidence intervals*

in the elderly (28 per cent of admissions in patients aged $\geqslant 60$ years). Moreover, there were two peak age groups for emergency admission: 10–29 years (31 per cent of patients) when the most common diagnoses were NSAP (51 per cent) and acute appendicitis (33 per cent), and 60–79 years (29 per cent of patients) when the common diagnoses were intestinal obstruction (25 per cent), NSAP (23 per cent), cholelithiasis (9 per cent), colonic diverticular disease (9 per cent), and various non-obstructing malignancies. Gilmore *et al* [12] also witnessed a bimodal age distribution in emergency surgical admissions although the causes of admission were not documented.

Less than half (47 per cent) of the patients in this study underwent a surgical operation but there was a 16 per cent incidence of unnecessary appendicectomy chiefly due to misdiagnosis of appendicitis in patients suffering from NSAP. The problem was greatest in young adults (22 per cent incidence in the age range 20–29 years) and particularly in young females, although a minority were found to have gynaecological pathology accounting for their symptoms. Previous studies have recorded an incidence of unnecessary appendicectomy ranging from 8 to 33 per cent[13] and it has been suggested that the accuracy of diagnosis may be improved either by the use of laparoscopy[14–16] or by the use of a computer database and application of Bayesian probability[8,9,17]. Neither method is widely used by general surgeons, and they were not used during the period of this study.

Gynaecologists regularly use laparoscopy in the diagnosis of pelvic or lower abdominal pain, and recent studies by general surgeons have suggested that laparoscopy has considerable value in the diagnosis of the acute abdomen. Thus, in a group of 36 young female patients presenting with clinical features suggestive of appendicitis, Deutsch *et al.*[15] avoided inappropriate laparotomy in 12 cases by the use of diagnostic laparoscopy, and Paterson-Brown *et al.*[16] observed that laparoscopy prevented an inappropriate clinical decision in six of 31 patients presenting with acute abdominal pain.

Computers aid the diagnosis of abdominal pain by providing probabilities for different diagnoses based on a comparison of the presenting clinical features in each case with a database of features associated with specific causes of abdominal pain. Single centre[8] and multicentre[9] studies suggest that such methods are of significant value in the diagnosis of abdominal pain but they have not found wide application, and a recent review[18] suggests that further research is required before computer-aided diagnosis can be widely implemented in the National Health Service in the UK. Perhaps such research should pay particular attention to the problems of diagnosis in young females with abdominal pain.

The highest proportion of perioperative deaths in this study (28 per cent) followed exploratory laparotomy for inoperable disorders such as massive intestinal gangrene resulting from superior mesenteric vascular occlusion or extensive abdominal carcinomatosis. Seymour and Pringle[19] have suggested that such patients should be discounted from mortality statistics because of their potentially non-viable status but it is possible that some perioperative deaths in patients with advanced abdominal malignancy might have been avoided by the use of laparoscopy rather than laparotomy. Like other surgeons[20,21], we have in our department used laparoscopy in the elective staging of pancreatic and oesophageal cancers, but we have no experience in the use of this technique in the assessment of malignancies presenting as an 'acute abdomen'.

Ruptured aortic aneurysm and perforated peptic ulcer, two of the least common presenting illnesses, proved to be the major causes of potentially avoidable perioperative death in this study.

Ruptured aortic aneurysm occurred in only 1·3 per cent of admissions but it was associated with a 71 per cent perioperative mortality rate. Specialist vascular units report an average hospital mortality rate of 40 per cent for this condition[22] with a range of 15–68 per cent[23], but the figure may be higher in non-specialist units and in patients aged >75 years[24]. The factors that influence the prospects of survival are accurate diagnosis, the transfer time to hospital, and the availability of skilled resuscitation and immediate, speedy surgery with an absence of technical errors[23,25]. The CEPOD report[10] recommended that all patients with aortic aneurysm should be admitted to specialist vascular units but this will not be possible in the foreseeable future due to the shortage of vascular surgeons and trainees[26]. It is our impression that many of the patients who died in Exeter were unsalvageable. Eight of the ten deaths occurred in patients aged >75 years and a significant proportion had coexisting cardiovascular disorders and underwent emergency surgery with an unstable circulation. However, it is not possible by retrospective analysis to establish the speed of transfer to hospital or the adequacy of the resuscitation or surgery. The operations were performed by surgeons of consultant or senior registrar status with experience in vascular surgery although the elective clinical interest of the unit is largely confined to gastrointestinal surgery. Anaesthetists of consultant or senior registrar status were involved in the resuscitation of the patients, and the survivors of surgery were nursed in the intensive therapy unit However, the results of this audit have prompted the development of a prospective study of ruptured aneurysm and a clearly defined strategy to minimize delay in the transfer of patients to the operating theatre.

Perforated peptic ulcer occurred in 2·5 per cent of admissions but it was associated with a perioperative mortality rate of 23 per cent and accounted for 16 per cent of the perioperative deaths in this study. There have been important epidemiological changes in the clinical presentation of perforated ulcer in recent years. The majority of patients are elderly and have acute ulcers, sometimes induced by non-steroidal anti-inflammatory drugs, and a significant proportion have coexisting medical disorders which present increased risks in surgical treatment. Recent studies of such cases have reported mortality rates in excess of 30 per cent[27–29] and it appears that a new strategy is required for the management of perforated ulcers in elderly subjects[29]. Risk factors in elderly patients such as delayed presentation, shock, and serious coexisting medical disorders are associated with an increased probability of perioperative death and there may be a case for a trial of non-operative treatment in such cases[30]. It is possible that some of the patients in this study might have survived if they had not been subjected to surgery but a prospective study is required to determine the value of case selection based on risk stratification. However, it is apparent that there is now a very limited place for definitive ulcer surgery in the management of perforation Most patients have acute pyloroduodenal perforations and these can be managed by simple suture of the perforation and administration of histamine antagonist drugs[31]. Interestingly, such treatment did not prevent two reperforations in this study although both patients received intravenous ranitidine during surgery and after operation. Perhaps faulty surgical technique was responsible for the outcome in these cases.

Urgent colonic resections were associated with a 9 per cent perioperative mortality rate, a rate which is substantially lower than the 17–38 per cent mortality rates reported in recent studies[7,32,33]. The majority of deaths in this study occurred in elderly patients with faecal peritonitis resulting from perforated diverticular disease or perforated colonic carcinoma, despite resuscitation, expeditious surgery, intensive care, and antibiotic therapy. However, one death due to pulmonary embolism may be attributed to the absence of low-dose heparin prophylaxis in a subject with an increased risk of this complication.

The resource implications of patients admitted with abdominal pain were identified in the study of bed utilization. The average duration of stay increased with age, and patients in the age group 70–79 years had the greatest bed occupancy (23 per cent of the total inpatient days) In a study of elective and emergency admissions to surgical wards, Seymour[34] found that the duration of stay increased progressively after the age of 64 years and patients aged ⩾75 years remained in hospital for a mean of 10 days. There is a certain sense of inevitability about such observations in the elderly. However, this study revealed that at least 20 per cent of elderly patients admitted as abdominal emergencies had a diagnosis of NSAP, and these patients also remained significantly longer in hospital by comparison with younger patients with NSAP. It is not clear if the elderly patients had more persistent pain or if the delay in discharge was due to uncertainty on the part of the clinicians with regard to the diagnosis. It is apparent that the elderly patients were more often subjected to radiological and endoscopic examinations, and such caution is perhaps justified since DeDombal *et al.*[35] found that malignant disease was the cause of NSAP in 10 per cent of admissions aged >50 years. Nevertheless, the group of elderly patients with NSAP deserves further study even if the outcome is simply more expeditious investigation and earlier discharge from hospital.

Various methods of self-assessment have been recommended for quality assurance in general surgery[10,36], and the type of audit described in this study has considerable educational value. It enables the clinician to determine the proportional risks attached to different types of surgery and disease and the attendant resource implications; and it permits a more informed discussion of the case material presenting in weekly mortality and morbidity meetings. However, the value of audit in quality assurance can be gauged only by ongoing continuous studies which demonstrate actual improvements in patient care, and manual methods of audit are too laborious for the frequent analyses required in such studies. There is a need for the careful planning of software programs and the development of computerized systems of audit in each health district. These could be developed on existing microcomputer programs[37] or, preferably, as part of a new Department of Health regional strategy for computer studies

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Acute pancreatitis and pancreatic fistula formation

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The cause, management and outcome of 23 patients with a pancreatic fistula following acute pancreatitis are reviewed. Nineteen patients developed an external fistula following necrosectomy or drainage of a pancreatic abscess or pseudocyst; four of these patients died. In the 15 survivors spontaneous closure occurred in 11 cases with low output fistulae; operative intervention was needed in the four cases with high output fistulae. Four patients with internal fistulae had not undergone previous surgery; two of them had a pancreaticopleural fistula with associated pancreaticogastric fistulae, while two had pancreatic ascites. All four of these patients required surgical intervention and one died.

Keywords: Pancreatic fistula, pancreatic ascites, acute pancreatitis

Pancreatic fistulae follow pancreatic duct disruption and may develop as a complication of pancreatic disease or injury. If disruption occurs during an attack of acute pancreatitis the escaping fluid may be walled off by the surrounding viscera to form a pseudocyst or an abscess may develop Fistula formation may follow surgical intervention for necrosectomy, or drainage of an abscess or pseudocyst. Fistulae may drain spontaneously into adjacent hollow viscera or communicate with the body surface externally. Less frequently, the duct disruption or rupture of a communicating pseudocyst remains free leading to pancreatic ascites or pleural effusion[1–3].

We present our experience of 23 patients with pancreatic fistulae that developed following an attack of acute pancreatitis; all were treated in Glasgow Royal Infirmary between January 1971 and July 1988.

Patients and methods

A fistula is usually defined as a communication between two surfaces lined by epithelium For the purpose of the present review the term is used to encompass communication between the pancreatic duct and the skin (external fistula), between the pancreatic duct and hollow viscera, and between the pancreatic duct and the peritoneal or pleural cavities (internal fistula). Duodenal fistulae are not included Patients were included in this review if the presence of a fistula was confirmed by a fistulogram or endoscopic retrograde cholangiopancreatography (ERCP) or if the output contained an amylase concentration higher than that of serum. External fistulae were classified as high output if the volume collected exceeded 200 ml per day. The aetiology of the acute pancreatitis and the number of positive prognostic factors were recorded[4]. The timing of onset of the fistula in relation to any previous operation or attack of pancreatitis was noted. The fistula was then classified as postoperative or spontaneous

Review of the prospectively documented experience of acute pancreatitis in Glasgow Royal Infirmary between January 1971 and July 1988 showed that 23 patients had fulfilled the above criteria Six of the patients had been referred from other institutions for management of necrotizing pancreatitis or pancreatic abscess The remaining 17 patients had been admitted initially to Glasgow Royal Infirmary

Of the 23 patients, 14 were men and nine were women, with a mean age of 40 years (range 17–67 years). Pancreatitis was considered to have been due to gallstones in 12 patients, from whom stones were recovered at operation. Eight patients had alcohol-induced pancreatitis, one patient had a duodenal tumour, and no precipitating cause could be identified in two patients. Three of the patients with internal fistulae have been reported previously[5].

External fistulae

Nineteen patients had postoperative external fistulae discharging through an abdominal wound or drain site All had three or more positive prognostic factors denoting severe acute pancreatitis The fistulae followed necrosectomy (nine patients), drainage of pancreatic abscess (eight patients) and drainage of pseudocysts (two patients) Fluid amylase estimations were available in eight patients and concentrations ranged from 1300 to 292 000 units per litre. Fistulograms were performed in 12 patients and showed that four of them also had internal fistulae (two in the colon, one in the stomach and one in the proximal small intestine). Two patients had ERCP demonstrating disruption of the main pancreatic duct system in the body and tail of the gland. Another patient was found to have a completely transected pancreatic duct at necrosectomy. The diagnosis in the remaining four patients with external fistulae was based on the high amylase levels Four of the patients had high output fistulae.

Internal fistulae

Four patients had six internal fistulae. Two of them had pancreaticoperitoneal fistulae while two presented with pleural effusions caused by pancreaticopleural fistulae ERCP in all four patients showed disruption of the pancreatic duct and free passage of contrast medium into the peritoneal or pleural cavity It also showed pancreaticogastric fistulae in the two patients with pancreaticopleural fistulae. Aspiration of peritoneal fluid in the two patients with pancreatic ascites gave fluid amylase concentrations of 75 000 and 72 600 units per litre respectively. Pleural fluid amylase concentration (125 000 units per litre) was measured in one man with a pancreaticopleural fistula

Results

Management was classified as conservative or operative. Conservative management followed recognized guidelines. Fistula output was collected into a drainage bag and the skin around the fistula protected by stomadhesive. Fistula output was assessed and adequate fluid replacement given. Once the fistula was established and the patient's general condition stabilized, the fistula track was displayed radiologically. The requirement for intravenous nutrition was assessed. Antibiotics were withheld unless there was evidence of septicaemia or peritoneal sepsis. Any intraperitoneal abscesses were drained. Surgery was undertaken in patients with external fistulae when it was considered that the fistula would not close spontaneously on conservative treatment. Internal fistulae draining into hollow viscera did not require surgical intervention. However, fistulae draining into the peritoneal and pleural cavities were treated surgically after stabilization of the patient.

External fistulae

Four of the 19 patients with external fistulae died, three of them in the intensive care unit after necrosectomy. One patient, a 50-year-old man, died from multiple organ failure 30 days after necrosectomy and colectomy. At operation 2 days after admission he was noted to have a completely transected pancreatic duct. He was managed by open packing with daily and then alternate day pack changes. The pancreatic duct continued to discharge until his death. The second patient was a 36-year-old woman with gallstone pancreatitis who developed a pancreaticocolocutaneous fistula following necro-

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tizing pancreatitis and who required necrosectomy and colectomy. Two weeks later, she developed a pancreatic abscess that required drainage and open packing. She died suddenly of cardiac arrest 5 weeks after surgery; the pancreatic fistula was still discharging at the time of death. She seemed to be making a good recovery and was thought to have had a pulmonary embolus. Permission for post-mortem examination was not obtained The third patient was a 62-year-old man with gallstone associated necrotizing pancreatitis who developed a high output external pancreatic fistula following necrosectomy 3 weeks after admission. He had drainage of a peripancreatic and subphrenic abscess; 15 days later he died in multiple organ failure, 31 days after his first operation. The fistula was still present at the time of death. The fourth patient was a 40-year-old man with idiopathic pancreatitis who developed a pancreatic abscess. After drainage of the abscess he developed a postoperative low output fistula which was treated conservatively for 3 months. He then developed septicaemia which led to his death from multiple organ failure 10 days later

Spontaneous closure of the fistula occurred in 11 of the 15 surviving patients. All 11 patients had low output fistulae. The mean closure time for this group was 12·3 weeks (range 8–14 weeks). The only fistula-specific complication occurred in a 52-year-old woman with alcohol-associated pancreatitis who developed a fistula after drainage of an abscess. During conservative management she had an episode of bleeding from the fistula track, losing 70 ml of bright red blood over 4 h. There were minor repeated episodes of blood loss over the following 3 weeks but the fistula then closed spontaneously. There were no other instances of haemorrhage from the fistula.

Four of the 15 survivors required some form of operative treatment. All four had high output fistulae. A 22-year-old woman with gallstone pancreatitis developed a high output fistula after cholecystectomy and drainage of a large pancreatic abscess She also developed a pseudocyst in the head of the pancreas. After conservative therapy for 5 weeks, the somatostatin analogue SMS 201-995 (Sandostatin®, Sandoz Ltd., Basle, Switzerland) was used An initial intravenous infusion over 48 h was followed by 3 days administration of 100 μg Sandostatin subcutaneously three times a day. The fistula output ceased within 36 h, but 24 h later the fistula began to produce fluid for a further 12 h; thereafter output ceased completely. However, the pseudocyst in the head of the pancreas increased in diameter to 8 cm and became symptomatic. Operative cystduodenostomy led to complete recovery.

The three remaining patients had surgery for high output fistulae and all made an uneventful recovery. A 65-year-old man underwent distal drainage for a pancreatic abscess. He also had transduodenal resection of a large duodenal adenomatous polyp thought to have caused the pancreatic duct obstruction leading to his pancreatitis. A 27-year-old man underwent distal pancreatectomy 23 weeks after onset of a pancreatic fistula following alcoholic pancreatitis A 33-year-old man with gallstone pancreatitis had a Roux-en-Y cystjejunostomy 16 weeks after the development of a fistula following rupture of a pancreatic pseudocyst.

Internal fistulae

All four patients with an internal fistula came to surgery The one patient who died was a 60-year-old alcoholic man who presented with insidious onset of pancreatic ascites (amylase concentration 75 000 units per litre). ERCP showed complete rupture of the pancreatic duct in the midbody of the gland. The patient became very ill 48 h after paracentesis. At laparotomy he was found to have gross peritonitis following laceration of the proximal jejunum by the peritoneal lavage catheter He had distal pancreatitis with peripancreatic necrosis and obvious rupture of the main pancreatic duct. Distal pancreatectomy was performed, but the patient died 15 days after the operation in respiratory failure.

The second patient with pancreatic ascites was a 26-year-old woman with gallstone pancreatitis who had initially undergone laparotomy for abdominal pain and distension At that time the peritoneum contained 5 litres of ascitic fluid (amylase concentration 72 600 units per litre), and ERCP 15 days later showed rupture of the pancreatic duct in the body of the gland. At laparotomy 8 days after ERCP the pancreas was very soft and the site of leakage could not be identified. She made a good recovery after insertion of four soft sump drains and a feeding jejunostomy; the ascites did not recur.

Both patients with pancreaticopleural fistulae underwent distal pancreatectomy, performed 6 and 9 weeks respectively after development of pleural effusions. The first patient, a 28-year-old man, had no further accumulation while the second, a 17-year-old man, required three further pleural aspirations before his effusions resolved.

Discussion

Severe necrotizing inflammation develops in 5–15 per cent of patients with acute pancreatitis[6–9]. Many of these patients go on to develop infected pancreatic necrosis, pancreatic abscess or pseudocysts and there is current interest in the value of early surgical removal of infected necrotic material. Whether the pancreatic bed should be managed subsequently by irrigation[6], multiple drains[7] or open packing[8] is controversial. The incidence of pancreatic fistulae following such surgery ranges from 12 to 40 per cent[6–9]. The majority of these fistulae will close spontaneously as occurred in 11 of the 15 surviving patients with external fistulae in the present review. Skin care, fluid replacement, nutritional support and radiological delineation of the fistula form the cornerstones of conservative therapy, but the surgeon must have a low threshold for intervention to drain infected intra-abdominal collections.

Patients with high output fistulae, usually associated with proximal obstruction or irreversible distal gland disconnection, are more likely to come to surgery. Pancreatic resection along a line just proximal to the point of duct rupture is the usual treatment. A fistulogram may delineate pancreatic duct anatomy and identify the site of duct rupture before surgery If fistulography is unhelpful, ERCP may be used to define the pathological anatomy and plan the line of pancreatic resection

As Cameron *et al.*[2] have pointed out, internal pancreatic fistulae are probably underdiagnosed. Many patients are alcoholics, and their ascites is thought to be due to liver disease until the peritoneal fluid is checked for amylase and protein concentration[1–3,10,11]. The disrupted major pancreatic duct or related pseudocyst continues to discharge due to the absence of an active peripancreatic inflammatory response Free communication between pancreatic duct and peritoneal cavity leads to ascites which may be massive, as the pancreas normally produces over 1 litre of fluid per day If the rupture is situated posteriorly, fluid tracks into the mediastinum alongside the oesophagus or aorta. It can then rupture into the pleura resulting in effusion formation, or more rarely, the lung becomes involved with formation of a pancreaticobronchial fistula[12]. The lack of inflammatory response means that spontaneous closure is unlikely Protracted conservative therapy leaves the patient at risk of developing sepsis and it is now considered unwise to continue such treatment for more than 2–3 weeks. If conservative treatment is undertaken, it should include complete drainage of the ascites or pleural fluid and parenteral hyperalimentation. ERCP is essential to delineate the site of duct rupture or define the presence of a leaking pseudocyst in patients with such internal fistulae[5,10,12]

Pancreatic resection is indicated if surgery is needed following duct disruption in the body or tail of the pancreas, whereas Roux-en-Y cystjejunostomy or pancreaticojejunostomy can be undertaken for lesions in the head. One patient in the present series was successfully managed by insertion of soft sump drains when the site of the rupture could not be identified There is no need to extend the dissection of the fistula track into the chest in patients with a pleural fistula because disruption of the track in the course of pancreatic surgery prevents further passage of pancreatic fluid into the chest.

There has been interest over the years in attempting to accelerate fistula closure with agents such as atropine, diamox and radiotherapy[2]. Somatostatin and its analogues have also been employed, and 13 of 16 patients showed fistula closure following intravenous somatostatin infusion at a rate of 250 μg/h[13,14]. Kingsnorth *et al.*[15] showed no such benefit when using somatostatin in six patients with enterocutaneous fistula, including one with a pancreatic fistula. Pederzoli *et al.*[16] showed a significant decrease in the time of fistula closure in eight patients with high output fistulae treated with somatostatin and total parenteral nutrition, compared with 18 treated with parenteral nutrition alone. Ahren *et al.*[17] published a case report demonstrating the use of the somatostatin analogue SMS 201-995 in closure of a pancreatic fistula. Following fistula closure, their patient developed a pseudocyst in the head of the pancreas which required ultrasonographically guided needle aspiration. This is a very similar experience to that of the patient in the present series. The role of somatostatin in treatment is still not clear, but it may yet prove to be useful[18].

The mortality rate in the present series (22 per cent) is consistent with that of the other reports and reflects the severity of the underlying disease process. Four of the five deaths were due to multiple organ failure following necrotizing pancreatitis while the fifth death followed a complication of paracentesis. Only one patient died as a result of a septic complication of the pancreatic fistula itself. Prompt recognition of the fistula, supportive therapy, active investigation by fistulography and/or ERCP and timely intervention will give the best results in the management of pancreatic fistulae.

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Surgical treatment of chronic pancreatic cholangiopathy

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In a consecutive surgical series of 70 patients with chronic calcifying pancreatitis, 18 presented with fixed stenosis of the terminal common bile duct. Nine patients presented with jaundice and two had a palpable gallbladder. The most relevant laboratory datum in the series was a persistently high serum alkaline phosphatase level. Long tapering of the terminal common bile duct was the characteristic radiological sign in 45 of our patients. In five of the 18 cases compression of the terminal bile duct was due to cephalic pseudocysts. Hepaticojejunostomy-en-Y was the type of drainage chosen in 16 cases, and an end-to-side technique was used in 15 patients. Side-to-side choledochoduodenostomy was performed in two cases. In 14 patients, biliary drainage was associated with other surgical procedures on the pancreatic parenchyma. No postoperative complications due to the biliary drainage occurred in this series.

Keywords: Chronic pancreatitis, chronic pancreatic cholangiopathy, hepaticojejunostomy

Fixed stenosis of the terminal common bile duct (or chronic pancreatic cholangiopathy) is a relatively frequent non-metabolic complication of chronic calcifying pancreatitis. Its importance lies in the fact that it can favour the onset of cholangitis or secondary biliary cirrhosis, cause diagnostic confusion with pancreatic neoplasm, and cause persistent pain after direct operations on the pancreatic parenchyma.

The incidence of biliary stenosis secondary to chronic pancreatitis has been extremely variable in different reported series[1,2], ranging from 4 per cent[3] to 46 per cent[4]. This ratio may vary according to whether studies are based on a clinical[5], surgical[6], radiological[4] or autopsy series[7]. The condition must be distinguished from the slight, transient, hyperbilirubinaemia which may occur in patients with clinical episodes of acute inflammation in the course of chronic pancreatitis. In these circumstances, oedema often subsides with resolution of the acute inflammatory process and specific therapy is not required unless a major complication develops[8].

Fixed stenosis of the lower common bile duct due to chronic pancreatitis should be suspected whenever high levels of serum alkaline phosphatase persist, regardless of whether they are accompanied by a high serum bilirubin level[9,10]. The next step in investigation is cholangiography, whether percutaneous or endoscopic, although preference is now given to the latter as it can also demonstrate alterations of the pancreatic ductal system. Even though diagnostic uncertainty between chronic pancreatitis and cancer of the head of the pancreas is not frequent in experienced centres, there are cases in which doubt may remain even after intraoperative biopsy, so that the best biopsy, in such instances, is the resection specimen[11]. Opinion is also divided about the optimal method of treatment of bile duct stenosis in chronic pancreatitis[12–15]; the role of the various drainage procedures is debated, and there are those who advocate the Whipple resection for this condition[16].

This paper relates our experience with pancreatic cholangiopathy and its surgical treatment in a consecutive series of patients undergoing surgery for chronic pancreatitis.

Patients and methods

From January 1975 to October 1987 we operated on 70 patients with chronic pancreatitis. Eighteen of these patients presented with a non-metabolic complication of chronic pancreatitis, namely stenosis of the terminal common bile duct. Of this subgroup, 17 patients had an alcoholic aetiology; in one patient the cause of chronic pancreatitis was not identified. Thus, 26 per cent of the patients with a confirmed diagnosis of chronic pancreatitis had persistent extrahepatic obstruction of the biliary tract. There were 15 men and three women ranging in age from 31 to 64 years (mean 38·2 years).

Nine patients were clinically jaundiced on admission to hospital. In two cases there was a palpable gallbladder and one patient experienced intermittent pyrexia. The most relevant laboratory datum was a persistently raised serum alkaline phosphatase level, averaging 522 units/l (normal value 92 units/l), in all the patients of this series.

Before operation the biliary system was evaluated in eight cases by endoscopic retrograde cholangiopancreatography and, in one non-jaundiced patient, by intravenous cholangiography. In the other nine patients, radiological diagnosis was achieved by intraoperative cholangiography (*Figure 1*). Extreme dilatation of the common hepatic duct was only demonstrated on two occasions, while in the other patients the duct was slightly dilated or had a normal diameter. The long tapering terminal common bile duct characteristic of this situation was seen in 15 of our patients, but other radiological presentations may appear (*Figure 2*), as in three of our 18 cases. In these three cases some doubt remained after the cholangiography about the differential diagnosis; however, the surgical biopsy confirmed the diagnosis of chronic calcifying pancreatitis rather than neoplasia.

In ten patients, bacteriological culture of the bile was obtained and revealed growth of *Escherichia coli* in four cases and *Proteus vulgaris* in one. In the other patients for whom bacteriological culture study was undertaken there was no growth.

In five of the 18 patients (28 per cent) compression of the terminal

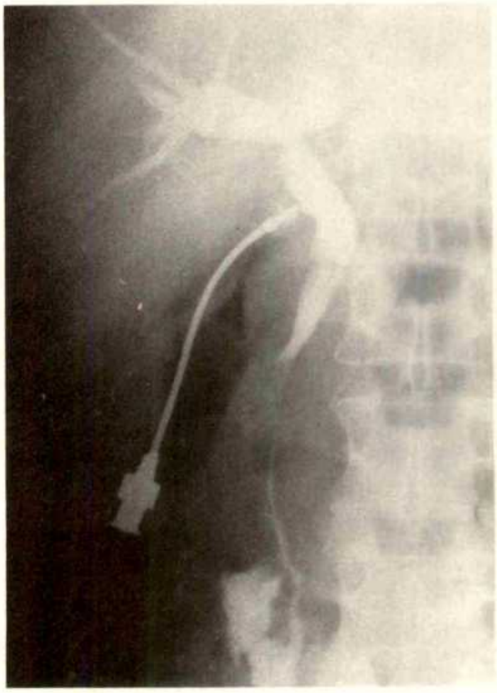

Figure 1 *An intraoperative cholangiogram demonstrating the long tapering of the terminal bile duct, with non-dilated duct above the stenosis*

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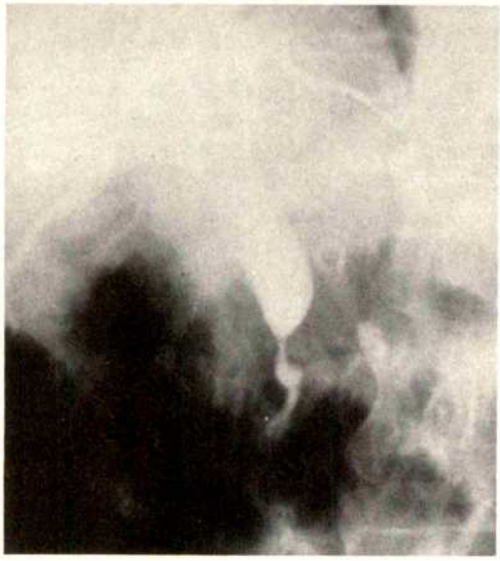

Figure 2 *An endoscopic retrograde cholangiopancreatogram demonstrating stenosis of the terminal bile duct and an irregular dilatation above the stenosis, caused by chronic pancreatitis*

common bile duct was due to the presence of pseudocysts in the head of the pancreas, and in the others it was considered to be due to calcification and/or fibrotic nodules caused by chronic pancreatitis. In 14 of the total group of 70 patients (and here we are including those with pseudocysts of the head of the pancreas, as well as those having biliary drainage) side-to-side pancreatojejunostomy was also performed (in 13 cases) and subtotal pancreatectomy (in one case). In three patients the biliary–digestive anastomosis was performed as an isolated procedure, while two of these patients had undergone pancreaticojejunostomy, 6 years previously in one case and 9 months earlier in another. Finally, one patient underwent biliary drainage without previous or concomitant pancreatic operation; he was jaundiced, with a serum alkaline phosphatase level four times the normal value, had pancreatic calcifications and was diabetic, but did not have painful chronic pancreatitis.

Hepaticojejunostomy using a Roux-en-Y loop was the type of drainage chosen in 16 cases; the anastomosis was end-to-side in 15 patients and side-to-side in one (due to technical difficulties in isolating the hepatic duct from the portal vein, secondary to the inflammatory process and associated portal hypertension). Side-to-side choledochoduodenostomy was performed in two cases in which the bile duct had thickened and dilated walls. In those patients who had not been submitted previously to cholecystectomy, the gallbladder was removed.

Results

There was no immediate postoperative complication attributable to the biliary drainage procedure in this group of patients. On follow-up (mean duration 3·2 years), 14 patients are alive at the time of this report; levels of serum alkaline phosphatase are slightly elevated in five patients (mean value 183 units/l) and are normal in the others. Of the surviving patients, 12 continue to abuse alcohol but have not shown clinical evidence of biliary obstruction. The long term mortality rate of 22 per cent (four of 18 patients) was attributable to progression of the underlying disease and not to the failure of the biliary–digestive anastomosis.

Discussion

The actual prevalence of chronic pancreatic cholangiopathy remains unknown, as series of patients with different types of pancreatitis are included in the same study. For example, the recent study of Stabile *et al.*[17] describes a prevalence of 4 per cent in 910 patients with chronic pancreatitis. On the other hand, it does not mention the method employed to diagnose pancreatitis, and there is no doubt that in many instances it is based on clinical rather than surgical diagnosis. The study of Aranha *et al.*[3] shows a similar prevalence to that reported by Stabile *et al.*, where cases with fixed stenosis of the terminal common bile duct were taken from a large series of patients with a clinical diagnosis of pancreatitis. The other extreme is a study of Wisloof *et al.*[4] where 46 per cent of the cases of chronic pancreatitis had stenosis of the terminal bile duct. Perhaps this high rate is due to the selection of patients, because it refers to a series with a radiological diagnosis of chronic pancreatitis.

In studies consisting mainly of surgical patients[6,8,15] admitted in order to treat severe pain or non-metabolic complications of chronic pancreatitis, the percentage of patients with pancreatic cholangiopathy would be higher than that reported by many authors[1,3,17,18]. This is probably due to the fact that these are patients with pancreatitis of sufficient severity to merit surgical treatment. Furthermore, chronic pancreatitis is a disease which can manifest itself in various ways in different places, despite a common aetiology[13,19–21].

Stenosis of the terminal common bile duct in chronic pancreatitis can bring about important hepatobiliary complications, such as cholangitis and secondary biliary cirrhosis. Warshaw *et al.*[22] demonstrated that waiting for evidence of advanced biliary disease to develop in patients with biliary stenosis due to pancreatitis increases the incidence of secondary biliary cirrhosis. On the other hand, Yadegar *et al.*[23] suggested that patients with high alkaline phosphatase levels and pancreatitis must be followed up with biannual liver biopsies to allow early detection of pathological changes suggestive of secondary biliary cirrhosis, so that surgery can be instituted. We believe that, in addition to the difficulties of effective biannual follow-up of patients with chronic pancreatitis, repeated biopsy of a cholestatic liver is not without risk.

When compression of the terminal common duct is due to a non-calcified inflammatory mass on radiological study, cancer of the pancreas must always be excluded. The experienced pancreatic surgeon may still have diagnostic doubts even when the clinical, laboratory, radiological and intraoperative findings are considered together. Every attempt should be made to obtain the definitive diagnosis during operation and the surgeon must be prepared to resect a mass in the head of the pancreas at the first operation if doubt persists, as secondary operations in this area make dissection dangerous and difficult. Even though the final pathological diagnosis proves to be chronic pancreatitis, the literature[16,24] suggests that duodenopancreatectomy is an effective operation because it decompresses the splenoportal system, relieves cholestasis and avoids any future duodenal obstruction. Furthermore, it resects the inflammatory mass in the head of the gland, which is considered by some to be the pacemaker of chronic pancreatitis[25]. It is important to emphasize that all pancreatic operations should be planned in advance and proper, informed consent obtained from the patient and the relatives[26].

In 28 per cent of the cases in the present series there was a pseudocyst in the head of pancreas which was drained into the loop used for pancreatojejunostomy. Yadegar *et al.*[23] present cases of such cysts with compression of the terminal bile duct and cholestatic syndrome, where cystenterostomy resulted in the disappearance of biliary obstruction. On the other hand, Machado *et al.*[6] report two patients in whom no biliary drainage was initially performed, but who later developed jaundice. It is well known that relief of the causative factor may allow the biliary obstruction to recede, and intraoperative cholangiography is recommended to verify the patency of the biliary tree after cystenteroanastomosis[23]. It has been our practice to perform a bilioenteric anastomosis using a Roux-en-Y loop in this situation if the preoperative clinical and laboratory data are consistent with cholestasis and if at operation there proves to be dilatation of the common hepatic duct. Even though some of these patients may not have fixed stenosis, we justify our procedure on the basis that the risk of not performing biliary drainage is certainly greater than that of prolonging the operation time.

Even though choledochoduodenostomy is the treatment of choice of a large number of authors[9,12,17,23,27] when faced with chronic pancreatic cholangiopathy, this operation has some drawbacks. To remain patent over a long period, the anastomotic diameter must be at least 1·5cm[28], and such ductal dilatation is not the rule in chronic pancreatic cholangiopathy. Choledochoduodenostomy performed with a thin-walled bile duct, as is common in this condition, can be complicated by leakage and duodenal fistula formation. Elliot[29] has described cases in which there was the need to revise a side-to-side choledochoduodenal anastomosis in patients who had food packed in the bile duct beneath the anastomosis. Although some authors consider that the 'sump syndrome' is more theoretical than real[17,30,31], they recommend performing this anastomosis in an end-to-side manner. On the other hand, the great advantage of this operation, as we see it, is the speed and ease of its performance when a side-to-side technique is used. If the surgeon has to dissect and separate the bile duct from the portal vein in order to perform an end-to-side anastomosis, the advantages discussed above are lost.

Another method of treatment of chronic pancreatic cholangiopathy is cholecystjejunostomy[13,15]. As these patients' life expectancy is long, cholecystenterostomy should be reserved for when there is particular technical difficulty, as when there is associated portal hypertension. This anastomosis really depends on the diameter of the cystic duct and not on the diameter of the anastomosis performed; death due to postoperative cholangitis has been reported[10]. Dayton *et al.*[32] suggest that the gallbladder as a route for biliary drainage should be reserved for terminal malignant disease, when the patient's life expectancy is short.

In the majority of our patients we performed end-to-side hepaticojejunostomy Roux-en-Y. This operation avoids the sump syndrome and does not involve the duodenum in the anastomosis, which can occasionally be obstructed or involved by the pancreatic inflammatory process. Although hepaticojejunostomy Roux-en-Y is said to increase the incidence of postoperative peptic ulcer[33–35], many publications do not support this contention[36–40]. We should not expect biliary-enteric drainage to relieve the painful symptoms of chronic pancreatitis, as the aim of these operations is to prevent cholangitis and secondary biliary cirrhosis and to treat cholestasis which follows compression of the terminal bile duct by an inflammatory pancreatic mass.

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Acute pancreatitis after renal transplantation

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Post-transplantation pancreatitis is an infrequent complication with a high risk of mortality. In a 7-year period, there were five patients who had documented pancreatitis out of a total of 488 renal homograft recipients, an incidence of 1 per cent. Two cases occurred in patients with an orthotopic transplant, one of them as a result of surgical injury of the pancreas and the other as a consequence of cytomegalovirus infection. The third case was an acute pancreatitis of hypercalcaemic origin, the fourth patient developed postoperative pancreatitis and acute acalculous cholecystitis, and the fifth had acute pancreatitis and sepsis associated with cytomegalovirus infection. Three patients died as a direct result of the complication. The mean incidence and mean mortality rate of post-transplantation pancreatitis, as determined from our review of the literature of the last 15 years, are 2·3 and 61·3 per cent, respectively; these are similar to the figures found up to 1970 of 1·7 and 52·2 per cent. A multiplicity of factors present in the uraemic patient may be responsible for the continued frequency of post-transplant pancreatitis despite advances in surgical technique and immunosuppressive therapy.

Keywords: Renal transplantation, acute pancreatitis, hypercalcaemia, immunosuppressive therapy, cytomegalovirus infection

Acute pancreatitis is an infrequent but severe complication of renal transplantation. In a review of the literature up to 1970, there were 23 reported cases of pancreatitis with 12 deaths in 1321 renal allograft recipients, an incidence of 1·7 per cent and a mortality rate of 52 per cent[1]. These figures have not changed 15 years later; a recent survey documented an incidence of 2·3 per cent and a mortality rate of 61·3 per cent in 3253 renal transplantation recipients[1–15] (*Table 1*). These data highlight acute pancreatitis as an uncommon but often fatal complication in renal transplant recipients, despite recent advances in surgical technique and immunosuppressive therapy. A multiplicity of factors present in the uraemic patient may be responsible for the development of pancreatitis, which makes it difficult to identify the causative agent in most cases. We have diagnosed five instances of pancreatitis among 488 recipients of renal transplants in a 7-year period (1981–87).

Patients

Case 1

A 37-year-old man was diagnosed as having chronic renal failure secondary to membranoproliferative glomerulonephritis, which was confirmed by renal biopsy, in August 1975. In 1977, haemodialysis was instituted. A cadaver kidney was transplanted in April 1984 in an orthotopic position. Immunosuppression consisted of azathioprine and corticosteroids. Three intravenous prednisone pulses (200 mg each) were administered for rejection 12 days after transplantation. The patient complained of fever and left pleuritic chest pain 15 days after transplantation. Chest X-ray showed a small pleural effusion and ultrasonography revealed a left subphrenic collection. Antibiotic therapy was given and his condition improved. Clinical manifestations reappeared 30 days later and a second ultrasonograph disclosed a new subphrenic collection, 7 cm in diameter; needle aspiration produced 180 mm^3 of purulent fluid. The patient underwent surgical drainage of a small collection of pus in the lesser omentum and of a perirenal abscess. His clinical condition deteriorated 2 months later in spite of acceptable renal function. Computed tomographic (CT) scanning revealed a fluid collection in the lesser omentum. The patient was operated on and haemorrhagic necrotizing pancreatitis with a pancreatic abscess was found; the abscess was drained and a sample taken for histopathological examination. He remained septic and died on the fourth postoperative day. Pathological examination of the pancreatic biopsy showed the presence of acute haemorrhagic pancreatitis with cytomegalic inclusions (*Figure 1*).

Case 2

A 42-year-old woman was maintained on haemodialysis because of glomerular nephropathy from March 1975. In December 1983, she received a cadaveric renal allograft implanted in the right iliac fossa, but 30 days later the allograft was removed because of an irreversible episode of acute rejection. The patient received a living donor renal allograft on 23 January 1985 implanted in an orthotopic position. Immunosuppression consisted of cyclosporin and azathioprine. She complained of fever and left lumbar pain which radiated to the iliac fossa 12 days after transplantation. Ultrasonography disclosed a 200 mm^3 perinephric collection, which was evacuated under sonographic control. Analysis of the fluid showed an amylase and lipase content of 48 000 and 5200 units/l, respectively. Because of the persistence of clinical symptoms, a CT scan was performed which demonstrated recurrence of the perinephric collection. With the presumptive diagnosis of distal pancreatitis resulting from surgical injury, operation was undertaken and a peripancreatic collection was found (posterior to the body of the pancreas and close to the splenorenal anastomosis), with oedema and induration of the body and tail of the gland. The spleen was removed and a distal pancreatic resection performed. The postoperative course was uneventful and renal function remained stable. Histopathological examination of the surgical specimen showed inflammatory lesions compatible with acute pancreatitis. However, 16 months after surgery the patient was referred because of abdominal pain, fever and chills. Serum amylase and lipase levels were 529 and 379 units/l (normal value 200 units/l), respectively. A new episode of acute pancreatitis was diagnosed and supportive measures were instituted. Ultrasonography showed a cystic lesion in the body of the pancreas suggestive of a pancreatic pseudocyst. A cystogastrostomy was performed because of persistence of clinical symptoms and increased serum amylase and lipase levels. She developed an episode of gastrointestinal bleeding and died 30 days after operation.

Case 3

A 59-year-old man had undergone nephrectomy because of renal tuberculosis at the age of 29. Subsequently, stenosis of the bladder neck and recurrent pyelonephritis developed which caused progressive renal failure. In 1980, he was placed on haemodialysis. In August 1984 he received a living donor renal allograft which was implanted in the right iliac fossa and azathioprine and prednisone were administered. One month later, the left kidney was removed and he was treated with antituberculous medication (isoniazid and rifampicin). An increase in

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Table 1 *Review of the literature on post-transplantation pancreatitis*[7]

Year	Reference	No. of transplants	Acute pancreatitis No.	Acute pancreatitis %	Deaths (%)
1968	1	1321	23	1·7	52·2
From 1970 to 1989					
1972	14	106	2	1·9	50
1972	9	301	17	5·6	64·7
1972	10	86	5	6	100
1975	2	126	1	0·8	
1975	5	510	5	1·0	
1976	6		2	3	70
1977	11	168	5	3·0	60
1978	13	120	6	5	
1978	8	87	1	1	
1981	15		3		33
1982	4	405	5	1·2	100
1983	3	165	4	2·4	
1985	12	467	7	1·5	14
1987	7	224	8	3·6	38
1989	Present study	488	5	1·0	60
Total		3253*	76*	2·3*	61·3

* Cases reported up to 1970 not included

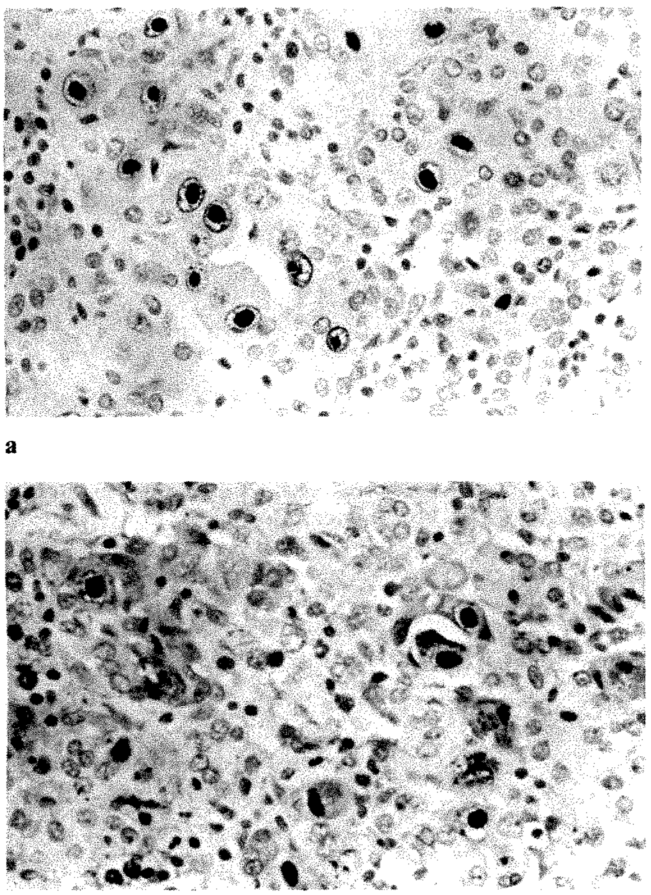

Figure 1 *Pancreatic biopsy showing destruction of ducts and acini with non-specific inflammatory infiltrate. Cytomegalovirus intranuclear inclusions demonstrated by* **a** *a monoclonal antibody (Dakopatts® m 757 (Dakopatts, Glostrup, Denmark)) and* **b** in situ *hybridization (Enzo® DNA probe (Enzo Diagnostics, New York, USA))* × *130*

serum levels of transaminase, γ-glutamyl transpeptidase, bilirubin and alkaline phosphatase were detected 15 days later, and all drugs except corticosteroids were discontinued. However, hepatic dysfunction associated with mild jaundice, pruritus, asthenia and weight loss persisted. Abdominal ultrasonography did not reveal dilatation of the intrahepatic biliary tree; liver biopsy disclosed cholestasis and hepatitis-like lesions. Tests for Australia antigen were negative, as were HBeAg and anti-HBe titres. The patient was discharged and maintained on corticosteroids. He was admitted again, 8 months after transplantation, because of ascites and mild encephalopathy. Renal function had remained stable. Physical examination revealed intense jaundice, ascites and grade I–II encephalopathy. Laboratory tests showed a serum bilirubin level of 16·7 mg/dl, serum glutamic oxaloacetic transaminase (SGOT) 630 units/l, serum glutamic pyruvic transaminase (SGPT) 410 units/l, alkaline phosphatase 530 units/l, γ-glutamyl transferase 157 units/l and Quick's test 55 per cent. Serum calcium levels were increased to 10·5–11·6 mg/dl. The patient was treated with cholestyramine resin, spironolactone and prednisone. Pain in the upper abdomen appeared suddenly 14 days after admission. Abdominal paracentesis obtained a clear non-infected transudate. The abdominal pain became worse, the general condition of the patient deteriorated, and dyspnoea and metabolic acidosis developed. Plain abdominal film showed dilatation of the transverse colon. Blood tests disclosed serum amylase levels of 1316 units/l, lipase 415 units/l, white blood cell count 19 600 mm^3 with 84 per cent segmented neutrophils and a serum calcium level of 16·8 mg/dl. In the ascitic fluid, the amylase level was 1119 units/l, the protein content 1 g/l, and the glucose content 66 mg/dl. The patient was transferred to the intensive care unit, but a few hours later, died of cardiorespiratory arrest and irreversible metabolic acidosis.

Case 4

A 53-year-old man, who had undergone left nephrectomy because of pyonephrosis in 1970, had been maintained on haemodialysis since May 1986 because of end-stage renal failure secondary to polycystic renal disease. In July 1987, he received a cadaveric renal allograft implanted in the left iliac fossa. Immunosuppression consisted of cyclosporin. The patient was reoperated on 24 h later because of a haemoperitoneum. Ascites developed in the immediate postoperative period. Laboratory data showed cholestasis with a serum direct bilirubin level of 9·7 mg/dl, total bilirubin 9·9 mg/dl, SGOT 33 units/l, SGPT 47 units/l, alkaline phosphatase 121 units/l, Quick's test 60 per cent and amylase 1930 units/l. Despite treatment with cyclosporin since transplantation, renal function deteriorated and haemodialysis was started 8 days later. Reduction of cyclosporin dosage resulted in normalization of serum creatinine. Abdominal ultrasonography, performed as a routine control examination, revealed an epigastric 15 × 9 cm collection which was drained under ultrasonographic control; 180 mm^3 of fluid were obtained. Culture of the fluid yielded growth of *Proteus mirabilis* and its amylase concentration was 30 000 units/l. The fluid collection persisted despite repeated punctures. In September 1987, the patient was operated on and acute acalculous cholecystitis and a pancreatic abscess were found. The abscess was drained and a cholecystectomy was performed. The patient had no postoperative complications and renal function remained stable.

Table 2 *Aetiologic factors in acute pancreatitis after renal transplantation*

Steroids
Hyperparathyroidism
Infection
Azathioprine
Surgical injury
Vasculitis and rejection
Uraemia
Alcohol
Biliary disorder
Hyperlipidaemia
Diuretics
Hypertension
Diabetes
Postoperative pancreatitis

Case 5

A 41-year-old woman was placed on haemodialysis because of end-stage renal failure secondary to chronic glomerulonephritis. She received a cadaveric renal transplant implanted in the right iliac fossa in March 1987. Immunosuppression consisted of azathioprine and corticosteroids. The patient complained of abdominal pain 32 days after transplantation. Blood tests showed increased serum amylase and lipase levels (460 and 234 units/l, respectively); 48 h later, the serum amylase concentration was 750 units/l, lipase was 191 units/l and the calcium level was 6·9 mg/dl. The diagnosis of acute pancreatitis was established and supportive measures were initiated. Abdominal ultrasonography showed the presence of peripancreatic fluid and parenchymal changes compatible with acute pancreatitis. The clinical condition progressively deteriorated, and blood tests disclosed an increase in cholestatic enzymes and decrease in the haematocrit. Fibreoptic endoscopy showed erosive oesophagitis and a duodenal ulcer. Consciousness was lost 18 days after the appearance of abdominal pain, as a result of encephalitis due to cytomegalovirus infection (elevated IgM-CMV antibody titres were detected). The patient died 3 days later of cardiorespiratory arrest. On autopsy, changes compatible with acute pancreatitis and sepsis due to cytomegalovirus infection were seen.

Discussion

In the present study, the incidence of post-transplantation pancreatitis was 1 per cent. However, three patients succumbed directly to this complication, a mortality rate of 60 per cent. In addition, one patient died 1 year after renal transplantation as a result of surgical treatment of a pancreatic pseudocyst that developed as a complication of the initial episode of acute pancreatitis; this results in an overall mortality rate of 80 per cent.

Table 2 details a series of factors that may contribute to pancreatitis in the complex setting of homotransplantation. Inflammatory changes in the pancreas have also been said to be very common in uraemia. Necropsy findings in cases of chronic renal failure have documented inflammatory pancreatic lesions in up to 52 per cent of patients who had not received immunosuppressive therapy or showed any clinical evidence of pancreatic disease[4,8,9,11,13,15].

The intensive immunosuppressive regimen used in renal transplant patients is a plausible explanation for post-transplantation pancreatitis[16]. Azathioprine can cause pancreatitis and rapid improvement has occurred after cessation of azathioprine with abrupt recurrence of pancreatic symptoms when treatment was reinitiated. Although several experimental studies have described corticosteroid-induced pancreatic changes (including pancreatic necrosis)[17], the relationship between steroids and pancreatitis is more difficult to establish clinically. Cyclosporin administration has not been associated with acute pancreatitis, although a direct toxic effect of this drug upon exocrine and endocrine pancreas has been observed[17–20].

The incidence of hyperparathyroidism is increased both in patients with renal transplants and in those with pancreatitis[21]. The question must be considered whether pancreatitis in patients with renal transplants is caused by increased levels of circulating parathormone or elevated serum calcium concentration[1,4,6–15]. In our third case, acute pancreatitis was certainly associated with high serum calcium levels.

That pancreatitis may be a form of 'rejection pancreatitis', in which the host forms an antibody reactive with pancreatic cellular surfaces, resulting in destruction of the pancreas, has been proposed. This possibility is supported by the evidence of signs of vasculitis in pancreatic biopsies from renal allografted patients[1,9–14].

Infection is a major cause of complications after renal transplantation and there is a well known relationship between pancreatitis and cytomegalovirus and herpesvirus. Conceivably, there could be direct colonization of the pancreas by such viruses[10]. Increased serum titres of anti-CMV antibodies as well as cytomegalic inclusions in the pancreas of renal transplant patients have been documented[22,23]. Elevated IgM-CMV antibody titres were found in two of our cases, as were cytomegalic inclusions.

Episodes of acute pancreatitis in renal allografted patients may also develop due to biliary tract disease and alcoholism, the commonest causes of pancreatitis in the non-uraemic population. It would seem prudent, in view of the known effects of alcohol abuse on the pancreas and the severity of the clinical disease in immunosuppressed patients, to screen potential recipients for a history of alcoholism and to proscribe alcohol following transplantation[12,13]. Although biliary tract disease is not the usual cause of acute pancreatitis in renal transplant patients, as the maximal age of patients undergoing renal transplantation has been rising steadily, ultrasound scans of the biliary tree are mandatory to exclude small calculi in cases of pancreatitis[12].

Miscellaneous causes of pancreatitis in postrenal transplant patients include uraemic hyperlipidaemia[24], hypertension[13], diabetes[15], administration of drugs (particularly thiazides)[8,9,11] and surgical pancreatic injury. Pancreatic injuries may occur during left nephrectomy and associated revascularization of the graft with the splenic vessels of the recipient. The technique of orthotopic renal transplantation uses the retroperitoneal approach to the splenic hilus via the lumbar region. The greatest danger in this approach is the possibility of damaging the pancreas when the renal and splenic vessels are dissected. However, of the total 132 orthotopic transplants performed in our institution, only the cases reported here (cases 1 and 2) had post-transplantation pancreatitis. These factors probably play minor roles in the overall postrenal transplantation population but each, together or in combination, may be significant for an individual patient.

The diagnosis of pancreatitis depends greatly upon an increase in the serum amylase level. When renal insufficiency occurs, evaluation of the serum amylase level can be difficult, as most patients with poor renal function have hyperamylasaemia. However, in renal failure, the amylase level is rarely greater than twice normal. The ratio of amylase clearance to creatinine clearance as determined on a random urine specimen or diagnostic paracentesis may be of great value in the diagnosis of patients who are suspected of having post-transplantation pancreatitis. Also, ultrasonography and CT scan deserve wide use in the diagnosis of pancreatitis. Even with good antibiotic cover, endoscopic retrograde cholangiopancreatography can be dangerous in cases of acute or recurrent acute pancreatitis, and an abscess may develop. Intensive medical management with particular attention to volume replacement and electrolyte balance is essential in the management of these patients. Early surgery has been advocated by some but the role of surgery in these very ill patients has yet to be defined and the risks of operation are extremely high. However, in cases of necrotizing pancreatitis, early operation may lead to increased survival. The difficulty here is to identify certain prognostic features that will select the high-risk patient who will benefit from early operation. Also, surgery is indicated if there is evidence of surgical injury of the tail of the pancreas, pancreatic abscess formation, or the development of a non-resolving pseudocyst.

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Surgical audit of patients undergoing common bile duct exploration for stone

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One hundred and sixty-four patients operated on for calculus disease of the common bile duct during the period 1977–85 were followed in a special clinic; the attendance for follow-up at 1, 3, 5 and 7 years was 90, 74, 60 and 54 per cent respectively. Eleven patients died during the study period (6·7 per cent), none of the deaths being attributable to biliary tract disease. The overall incidence of retained calculus was 2·4 per cent (four patients), but no cases of retained calculi were recorded in the last 4 years of the study; in this period, with the advent of choledochoscopy and fluoroscopic cholangiography, the incidence of the supraduodenal compared with the transduodenal approach to the common bile duct increased significantly ($P<0·001$). *Twenty-two of 56 patients (39 per cent) followed up for 5 years remained or became symptomatic after surgery, the majority of whom had underlying conditions unrelated to disease of the biliary or pancreatic tree. This specific follow-up clinic has been of value in the long-term audit of patients undergoing bile duct surgery for choledocholithiasis and it has verified that a change of policy from transduodenal to supraduodenal choledochotomy with preservation of the sphincter, and use of the choledochoscope and fluorocholangiography, produce better results.*

Keywords: Choledocholithiasis, choledochotomy, transduodenal sphincterotomy

The operative risks and the incidence of recurrent disease after surgery for calculus disease of the biliary tract are well documented and are based primarily on retrospective studies[1–7]. Many patients remain symptomatic despite no demonstrable evidence of recurrent disease[8,9], and apart from experimental studies[10] little is known about liver function as assessed by routine tests after biliary tract surgery. This prospective study of 164 patients, all of whom had undergone surgery for calculus disease of the common bile duct, aims to assess and correlate clinical outcome with serial postoperative liver function tests, knowing the operative findings and procedures.

Patients and methods

During the study period from January 1977 to December 1985, 164 consecutive patients (121 women, 43 men) who had undergone surgery for calculus disease of the common bile duct were referred to a designated biliary follow-up clinic. Patients' ages ranged from 19 to 94 years (mean age 59·4 years). Symptoms were recorded and serum bilirubin, alkaline phosphatase and glutamic oxaloacetic transaminase (SGOT) levels were determined. Patients were reviewed 6 months after their operation and if clinical examination and laboratory investigations were normal they were seen annually thereafter.

The operative procedures performed included supraduodenal choledochotomy (56), transduodenal sphincteroplasty (81), combined supraduodenal and transduodenal approach (11), and choledochoduodenostomy (16). *Table 1* compares the pattern of surgical approach to common bile duct calculi in the early (1977–81) and later (1981–85) parts of the study period. There was a significant reduction in the number of transduodenal compared with supraduodenal explorations ($P<0·001$). This coincided with the introduction of routine choledochoscopy and fluoroscopic cholangiography.

Fifty-three patients (32.3 per cent) had been jaundiced on initial presentation before surgery (serum bilirubin >17 μmol/l). Eighty-five (51·8 per cent) had elevated alkaline phosphatase levels (>100 units/l) and 59 (35·9 per cent) had elevated SGOT levels (>40 units/l) before operation. All patients with elevated concentrations of serum bilirubin or SGOT had an associate high alkaline phosphatase level.

Attendance for follow-up at 1, 3, 5 and 7 years was 90, 74, 60 and 54 per cent respectively. Five-year follow-up data were available for 56 of 94 patients operated on during the period 1977–81. seven patients died within 5 years of surgery, three failed to attend for any follow-up, and six were elderly (>70 years) but symptom-free at first review and follow-up by the general practitioner was thought to be more appropriate. The remaining 22 patients attended initially but for varying periods of time: one review only (four patients), two reviews (two patients), three reviews (nine patients) and four reviews (seven patients). All 22 patients were symptom-free and had normal liver function tests at last review.

Results

An 86-year-old woman died on the 12th postoperative day owing to biliary peritonitis following removal of a T tube. There were no other postoperative deaths. Eleven patients died during the study period (6·7 per cent), none of the deaths being attributable to disease of the biliary tract. The causes of death were myocardial infarction (four), cerebrovascular accident (three), gastrointestinal carcinoma (three) and bronchopneumonia (one).

Of the 56 patients with 5-year follow-up, 22 remained or became symptomatic (39 per cent). Eight patients developed complications related to common bile duct surgery (14 per cent). Residual calculi are known to have occurred in four patients in the series (2·4 per cent): all presented within 12 months of surgery and no instances of retained calculi have

Table 1 *Pattern of surgical approach to common bile duct calculi in early and later parts of the study period (1977–85)*

Operative procedure	1977–81	1982–85	Total
Supraduodenal choledochotomy	18	38	56
Transduodenal sphincteroplasty	63	18	81
Choledochoduodenostomy	8	8	16
Combined supraduodenal and transduodenal approach	5	6	11
Total	94	70	164

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been recorded since 1981. Three of the four cases followed supraduodenal choledochotomy and were removed at 6 weeks, 2 months and 4 months by heparin lavage via a T tube, by choledochoduodenostomy, and by transduodenal sphincteroplasty, respectively, the latter two after attempted endoscopic sphincterotomy. One case followed transduodenal sphincteroplasty and was removed endoscopically 10 months after operation; this patient later developed cholangitis and chronic pancreatitis and requires regular analgesia. Two other patients also developed cholangitis at least 6 months after transduodenal sphincteroplasty, one in association with septicaemia while the second subsequently developed pancreatitis with an associated pseudocyst. One patient developed obstructive jaundice following transduodenal sphincteroplasty, and this was found to be due to vegetable matter in the lower common bile duct. Another patient developed a common hepatic duct stricture, presumably related either to the cholecystectomy performed at the same time as transduodenal sphincteroplasty or to persistence of the initial narrowing related to the gallbladder empyema (Mirizzi's syndrome); this patient, to date, has responded to long-term antibiotics. Delayed complications related to surgery occurred in five of 63 patients who had undergone transduodenal sphincteroplasty compared with three of 18 patients who had undergone supraduodenal choledochotomy (not significant).

Ten of the 56 patients (18 per cent) developed pathology unrelated to biliary tract surgery which has responded to medical treatment. Liver function tests performed at the time of symptoms in these ten patients were normal (reflux oesophagitis, four patients; duodenal ulceration, two patients; diverticular disease, two patients; irritable bowel syndrome, one patient; pancreas divisum, one patient), and they were normal in the remaining four patients (7 per cent) who had symptoms but in whom investigations have revealed no underlying pathology.

Five patients who remained symptom-free after their operation had marginally elevated serum alkaline phosphatase levels at 5-year follow-up (mean 134 units/l, range 103–185 units/l). One patient had undergone removal of a retained calculus 6 weeks after supraduodenal choledochotomy. No obvious cause for the marginally elevated concentration of enzymes was found in the remaining four patients (transduodenal sphincteroplasty, three patients; choledochoduodenostomy, one patient).

Analysis of follow-up liver function tests in patients whose preoperative liver function tests were normal ($n=79$) revealed that at 6-month follow-up elevated levels of serum alkaline phosphatase occurred in 11 of 40 patients undergoing transduodenal sphincteroplasty (28 per cent) but did not occur in any of 26 patients who underwent supraduodenal choledochotomy ($P<0.005$, Fisher's exact test). At 5-year follow-up serum alkaline phosphatase had returned to normal concentrations in all but two of these patients. Analysis of follow-up liver function tests in patients whose tests were abnormal before surgery ($n=85$) showed no significant difference in the proportion with abnormal tests 6 months after transduodenal sphincteroplasty (16 of 41 patients, 39 per cent) compared with supraduodenal choledochotomy (13 of 30 patients, 43 per cent).

Discussion

Although there are a number of carefully reported retrospective studies documenting long-term clinical outcome after surgery for calculus disease of the common bile duct[1–6], prospective follow-up data are notably lacking[7]. Annual clinical assessment, serial liver function tests and further investigations, where indicated, have enabled us to provide detailed prospective data concerning long-term clinical and biochemical outcome after common bile duct surgery for benign disease. Ros and Zambon[9] have recently shown that a large proportion of patients remain symptomatic after simple cholecystectomy – many due to other gastrointestinal tract conditions. This study demonstrates that a large proportion of patients (39 per cent) also remain symptomatic after surgery for common bile duct stones and that many of these are likewise suffering from other gastrointestinal tract diseases.

The late mortality rate during the study period was high (6·7 per cent) but the majority of deaths occurred in the older age groups (mean age 78·1 years) and were chiefly due to degenerative arterial disease; this finding is similar to that reported by McSherry and Glenn[11] in a series of 11 808 consecutive patients operated on for non-malignant biliary tract disease.

The overall incidence of retained calculus (2·4 per cent) compared favourably with other series[4–6,12]. In our experience, the introduction of routine fluoroscopic postexploratory cholangiography and subsequently rigid choledochoscopy reduced the incidence of retained calculus and, apart from retained calculus, the procedure of supraduodenal choledochotomy[13] was associated with notably few long-term complications The transduodenal route is a technically more difficult approach and, although no postoperative deaths occurred in this series due to the procedure, transduodenal sphincteroplasty has been reputed to be associated with higher postoperative morbidity and mortality[1,4,6]. Furthermore, in our experience delayed cholangitis occurred in three of 81 patients following transduodenal sphincteroplasty and, although temporary, the procedure was also associated with a significantly higher incidence of elevated liver function tests 6 months after surgery in patients whose preoperative liver function tests were normal. These factors, together with the knowledge that a back-up endoscopic sphincterotomy service is readily available in the event of retained calculus, have resulted in a preference for a supraduodenal approach to the common bile duct except in circumstances such as the presence of multiple calculi in a non-dilated duct, a stone impacted at the papilla, re-exploration for a stone in the event of failed endoscopic retrograde cholangiopancreatography and sphincterotomy, or a short terminal common bile duct stricture with choledocholithiasis.

Transduodenal sphincteroplasty results in duodenobiliary reflux in some patients but it has been considered that reflux, provided it is combined with free egress from the biliary tree, is harmless. The increased incidence of transiently elevated liver function tests following transduodenal sphincteroplasty in this study, together with the pattern of long-term complications (cholangitis in three patients, two of whom also developed pancreatitis), raises the possibility that reflux of duodenal contents into the biliary tree may not be entirely harmless and suggests that patients who undergo transduodenal sphincteroplasty in particular should be reviewed regularly in the early postoperative period. Given that they are aware of the potential complications of such operative procedures, it would seem that follow-up by family practitioners is adequate and that a specific biliary follow-up clinic provides no significant benefit to individual patients in terms of long-term patient outcome.

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Mirizzi syndrome and cholecystobiliary fistula: a unifying classification

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A new classification of patients with Mirizzi syndrome and cholecystobiliary fistula is presented. Type I lesions are those with external compression of the common bile duct. In type II lesions a cholecystobiliary fistula is present with erosion of less than one-third of the circumference of the bile duct. In type III lesions the fistula involves up to two-thirds of the duct circumference and in type IV lesions there is complete destruction of the bile duct. A total of 219 patients were identified with these lesions from 17 395 patients with benign biliary tract diseases undergoing surgery. The incidence of type I lesions was 11 per cent, type II 41 per cent, type III 44 per cent and type IV 4 per cent. The majority had obstructive jaundice. In type I lesions, cholecystectomy plus choledochostomy is effective. In type II lesions, suture of the fistula with absorbable material or choledochoplasty with the remnant of gallbladder can be performed. In type III lesions suture is not indicated and choledochoplasty is recommended. In type IV lesions, bilioenteric anastomosis is preferred. Operative mortality rate increases according to the severity of the lesion, as does postoperative morbidity. During cholecystectomy, partial resection is recommended in order to extract the stones, visualize the common bile duct and define the type and location of the fistula. T tubes should be placed distal to the fistula.

Keywords: Cholecystobiliary fistula, Mirizzi syndrome, surgery

Mirizzi[1] originally described the syndrome that bears his name in 1948, when he found the following features in patients with gallstones: anatomical variation of a parallel cystic duct; gallstones impacted at the neck of the gallbladder or in the cystic duct; partial obstruction of the common bile duct secondary to compression by the stone or surrounding inflammation; recurrent cholangitis; and spasm of the circular muscular fibres in the hepatic duct Since his description, several isolated cases have been reported[2–11]. Communication between the gallbladder or cystic duct and the common bile duct is rarely referred to in the surgical literature[12–20]. After dealing with a number of patients with Mirizzi syndrome and cholecystobiliary fistula, we have come to realize that these are stages in the evolution of the same pathological condition.

The purpose of the present study is to define the incidence of the Mirizzi syndrome and cholecystobiliary fistula in a series of patients with gallstones, to propose a new unifying classification that includes both of these conditions, and to establish the surgical treatment for each stage of the pathological process.

Patients and methods

The present paper is a combination of a retrospective analysis (1976–82) and a prospective study (1983–87) of all patients operated on for gallstones in the Department of Surgery, University of Chile. A total of 17 395 patients were operated on during the entire period, so that approximately 1449 patients per year were submitted to cholecystectomy From this patient population, 219 patients (1 3 per cent) were considered to have Mirizzi syndrome and/or a cholecystobiliary fistula (see below).

A special procotol was designed for the study, in which 60 different parameters were included All data from each patient were documented on a chart and at the end of the study (July 1987), they were analysed by the IBM computer of the Faculty of Medicine (P240 IBM)

Pathological analysis

Each resected gallbladder was carefully examined histologically to exclude carcinoma All patients with benign strictures, stenosis of the sphincter of Oddi, carcinoma of the common bile duct and biliary–digestive fistulae were excluded from consideration Chronic cholecystitis corresponded to the presence of a gallbladder with a firm thick wall, and fibrosis. Histologically Aschoff–Rokitansky sinuses and mononuclear inflammatory cells were present. Acute cholecystitis corresponded to a gallbladder with fibrinous, shaggy, dull exudates with muscular engorgement with oedema and hyperaemia of the wall Histologically the presence of polymorphonuclear leucocytes was observed.

Acute suppurative cholangitis was defined during surgery as the presence of muddy bile or pus in the common bile duct, instead of clear green bile.

Definitions

For the present study, we have defined four evolving stages of the same disease and have classified them as follows (*Figure 1*):

1 *Type I lesion* external compression of the common bile duct due to a stone impacted at the neck of the gallbladder or at the cystic duct (i.e. the original Mirizzi syndrome)
2. *Type II lesion* presence of a cholecystobiliary fistula (cholecystohepatic or cholecystocholedochal) due to erosion of the anterior or lateral wall of the common bile duct by impacted stones, the fistula involving less than one-third of the circumference of the common bile duct
3. *Type III lesion* presence of a cholecystobiliary fistula with erosion of the wall of the common bile duct that involves up to two-thirds of its circumference
4. *Type IV lesion* presence of a cholecystobiliary fistula with complete destruction of the entire wall of the common bile duct

To determine the late results of treatment, a special questionnaire was completed with reference to pain, jaundice, loss of weight, tolerance to food, and whether the patient was content with the surgical result A total of 167 (76 3 per cent) of cases were followed in this way with a mean follow-up of 5 7 years (range 1–13 years)

For statistical evaluation, analysis of variance was used and $P<0.05$ was considered as statistically significant

Results

Among the 219 patients, 23 (10·5 per cent) had a type I lesion, 90 (41·1 per cent) a type II lesion, 97 (44·3 per cent) a type III

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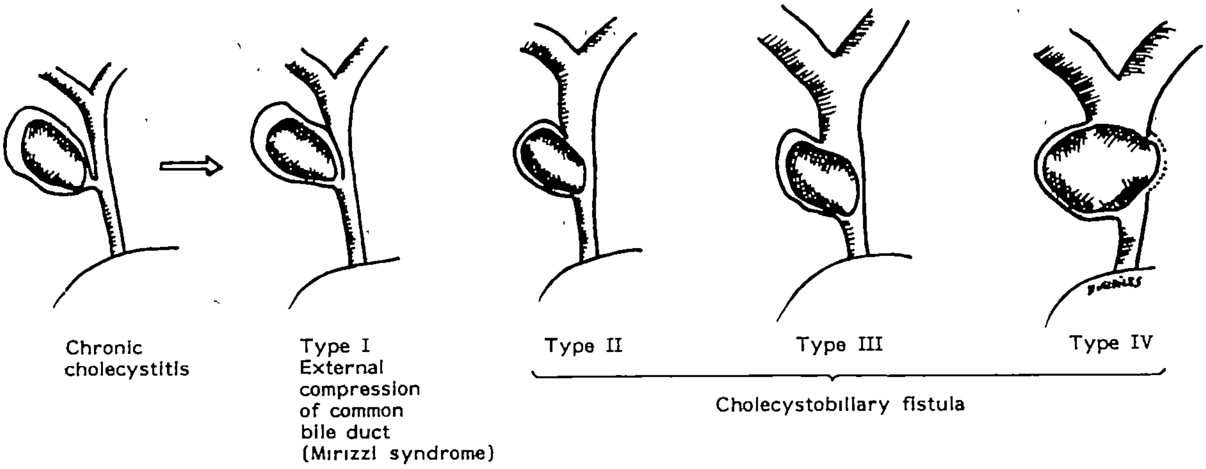
Chronic cholecystitis
Type I External compression of common bile duct (Mirizzi syndrome)
Type II
Type III
Type IV
Cholecystobiliary fistula

Figure 1 *Stages in the development of the Mirizzi syndrome and cholecystobiliary fistula*

Table 1 *Clinical findings on admission in 219 patients with external compression of the common bile duct or cholecystobiliary fistula*

	Classification			
Clinical findings	Type I ($n=23$)	Type II ($n=90$)	Type III ($n=97$)	Type IV ($n=9$)
Mean age (years)	44	42	53	62
Female (%)	65	77	77	100
Duration of symptoms >8 days (%)	43	43	39	55
Biliary pain (%)	100	94	97	100
Jaundice on admission (%)	83	84	92	67
Fever present for previous 5 days (%)	70	57	67	67
Rectal temperature >38°C (%)	35	33	53	34

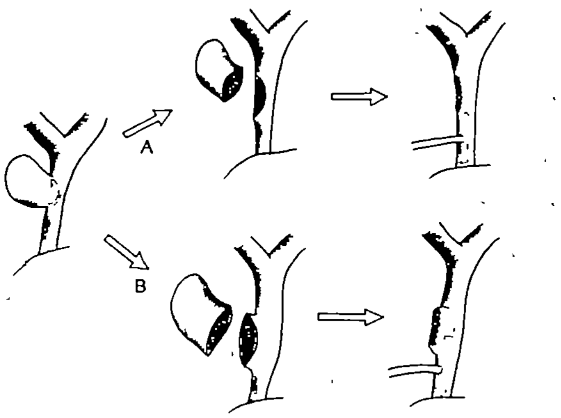

Figure 2 *Surgical alternatives for the repair of the common bile duct in patients with type II lesions Option A involves the simple suture, and in option B the cuff of gallbladder is used for choledochoplasty*

lesion and 9 (4·1 per cent) a type IV lesion. The main clinical findings in all cases are shown in *Table 1*. There was an increasing mean age in patients with type III and IV lesions. Almost all cases with type I, II and III lesions had a typical clinical picture of obstructive jaundice, but this was present in only six of the nine cases with type IV lesions

Previous oral cholecystography had been performed in 37 patients, showing no gallbladder filling in any patient. Ultrasonography was performed in 67 cases, demonstrating gallstones in all and a dilated proximal common bile duct in 54 of the cases. A type I lesion was suspected in six cases and a biliobiliary fistula in 12 patients

The main surgical findings in the gallbladder in the 219 cases are demonstrated in *Table 2*. Acute cholecystitis was more frequent in type I lesions, with multiple gallstones in approximately two-thirds of the cases. Chronic cholecystitis was frequently observed in patients with type II, III and IV lesions. The cystic duct was absent in all patients with type IV lesions and in two-thirds of patients with type II and III lesions. Stones were absent from the common bile duct in 92 per cent of cases with type I lesions and from 56 per cent of those with type IV lesions. In some patients with type II, III, and IV lesions, intrahepatic stones were also present. Acute suppurative cholangitis was more common in patients with type IV lesions.

Cholecystectomy was performed in all 219 patients, but was frequently partial or incomplete in patients with type II and III lesions, when a remnant of gallbladder was left in order to perform a choledochoplasty (*Table 3*). The surgical treatment in patients with type II lesions was most often suture closure (*Figure 2*) of the fistula (chromic catcut 4-0 or Vicryl® (Ethicon Ltd., Edinburgh, UK) 3-0) leaving a T tube distal to the closure for at least 2 months. In a quarter of type II patients choledochoplasty was performed, especially when the fistula was large. The most frequent method of repair of the fistula in type III lesions was also choledochoplasty using the cuff remnant of the gallbladder. The surgical treatment of patients with type IV lesions consisted of an end-to-end repair in five cases, a biliary enteric anastomosis in three, and a double hepaticostomy in one case.

The size of the cholecystobiliary fistula is shown in *Table 4*. Most patients with type II lesions had a fistula $\leqslant 10$ mm in diameter while, in patients with type III and IV lesions, the fistula was often larger.

Postoperative course is shown in *Table 5*. There was an increasing mortality rate, which was significantly greater when patients with type III and IV lesions were compared with other groups ($P < 0{\cdot}02$). The late results in the 204 patients discharged from the hospital are shown in *Table 6*. Two patients with type

Table 2 *Surgical findings at operation in patients with external compression of the bile duct or cholecystobiliary fistula*

Findings	Classification Type I (*n*=23)	Type II (*n*=90)	Type III (*n*=97)	Type IV (*n*=9)
Histology				
Chronic cholecystitis	9	54	65	7
Acute cholecystitis	14	36	32	2
Number of stones				
Absent	0	18	10	1
Solitary	7	17	29	3
Multiple	16	55	58	5
Diameter of cystic duct				
Absent	4	56	68	9
<5 mm	16	22	12	0
>6 mm	3	12	17	0
Diameter of common bile duct				
<12 mm	16	26	28	2
13–20 mm	7	50	56	4
>21 mm	0	14	13	3
Common bile duct stones				
Absent	21	20	37	5
Present	2	70	60	4
Acute suppurative cholangitis	4	32	50	6

Table 3 *Surgical procedures in patients with external compression of the common bile duct or cholecystobiliary fistula*

Operation	Classification Type I (*n*=23)	Type II (*n*=90)	Type III (*n*=97)	Type IV (*n*=9)
Biliary tract				
Cholecystectomy	6	0	8	4
Cholecystectomy plus choledochostomy	17	90	89	5
Fistula management				
Suture	0	66	5	0
Choledochoplasty with remnant of gallbladder	0	24	83	0
End-to-end anastomosis	0	0	1	5
Bilioenteric anastomosis	0	0	8	3
Hepaticostomy	0	0	0	1

Table 4 *Size of the cholecystobiliary fistula at operation in 196 patients*

Size of fistula (mm)	Classification Type II (*n*=90)	Type III (*n*=97)	Type IV (*n*=9)
≤10	60	21	0
11–20	29	51	1
21–30	1	14	2
>31	0	11	6

I lesions developed a benign stricture 3 and 4 months after surgery, and underwent hepaticojejunostomy with good results. In patients with type II and III lesions, 4 per cent developed a benign stricture within a mean interval of 12 months after surgery. All patients with type IV lesions, as well as the patient with a type III lesion in whom end-to-end repair was performed, developed a benign stricture 4 months after surgery; hepaticojejunostomy was performed in all cases with a good clinical outcome to date.

Discussion

The Mirizzi syndrome as originally described consisted of the combination of a stone impacted at the neck of the gallbladder or cystic duct and a functional disorder of a putative sphincter within the common hepatic duct, but without any lesion of the common bile duct[1]. Mirizzi postulated that a number of factors might trigger or predispose to contraction of this 'sphincter', such as inflammation, aberrant vessels or stones impacted in the cystic duct. External obstruction of the bile duct following impaction of a stone in the cystic duct with associated inflammation was described by Kehr in 1905 and by Ruge in 1908 as a rare form of obstructive jaundice[14]. It is now well known that there is no sphincter within the hepatic duct, and the jaundice seen in these patients is due to external compression secondary to impaction of a stone at the neck of the gallbladder or cystic duct. Mirizzi described seven cases with this syndrome drawn from 4000 patients operated on for gallstone disease[21]. Dietrich, cited in References 2, 10 and 11, reported in 1963 that a parallel cystic duct was present in 18 per cent of patients with gallstones studied by operative cholangiography. However, this was observed in only 1·8 per cent of 5800 patients studied by Puente[22] in our country.

Treatment of the Mirizzi syndrome is based only on the removal of the initiating factors, namely the inflamed gallbladder, cystic duct and impacted stone. The common bile duct should be visualized and explored, if necessary, to exclude other causes of obstructive jaundice. Most inflammatory strictures will return to normal when the inflammatory process resolves, as occurred in 16 of our 18 followed cases with type I lesions. T-tube insertion will ensure biliary flow and decompression during the healing process. We agree with Lubbers[2]

Table 5 *Postoperative course in patients with external compression of the common bile duct or cholecystobiliary fistula*

	Classification			
Outcome	Type I ($n = 23$)	Type II ($n = 90$)	Type III ($n = 97$)	Type IV ($n = 9$)
Postoperative morbidity	3 (13)	9 (10)	13 (13)	4
Haemoperitoneum	0	2	2	0
Bile peritonitis	1	3	1	1
External biliary fistula	2	2	9	3
Subphrenic abscess	0	2	1	0
Operative mortality within 30 days of operation	0	2 (2)	12 (12)	1
Residual stones	2	16	3	0

Figures in parentheses are percentages

Table 6 *Late results at follow-up of patients with external compression of the common bile duct or cholecystobiliary fistula*

	Classification				
Follow-up status	Type I ($n = 23$)	Type II ($n = 88$)	Type III ($n = 85$)	Type IV ($n = 8$)	Total ($n = 204$)
Asymptomatic	16	62	54	3	135 (66)
Benign stricture	2	3	4	3	12 (6)
Died owing to biliary disease	0	3	1	1	5 (2)
Lost to follow-up	5	20	26	1	52 (25)

Figures in parentheses are percentages

that the term Mirizzi syndrome could now be abandoned, as it is only the first stage of a more complex process, as has been shown in our study.

Cholecystobiliary fistula is a rare entity Puestow[18] described it for the first time in 1942, when he published details of one case in 16 patients with spontaneous internal biliary fistulae. Later, Behrend and Cullen[14] described it as a separate entity in three patients with cholecystocholedochal fistula. Mirizzi[16] described four cases in 1954 and others have published descriptions subsequently[23,24]. Some authors in our country have described this type of biliary fistula in 0·1–0·5 per cent of all patients submitted to surgery for gallstones[11,12]. Corlette and Bismuth[19] have presented 24 cases treated in a 15-year period and propose a classification based on whether patients have a cystic duct. In our experience the majority of patients did not have a cystic duct and so this classification has little use in surgical practice.

It is important to establish the diagnosis of fistula before operation, in order to plan the surgical procedure. In our prospective study, which began in 1983, ultrasound proved very useful in this regard and we doubt whether CT scanning will be of more value. Preoperative cholangiography is valuable and we have used mainly the percutaneous transhepatic route because endoscopic retrograde cholangiopancreatography (ERCP) has become available only recently. However, in addition to preoperative diagnosis, ERCP also allows drainage to relieve cholangitis and may well improve the eventual surgical results[25–27].

We consider that the so-called Mirizzi syndrome and cholecystobiliary fistula are different evolving stages of the same disease process In patients with stones impacted at the neck of the gallbladder or cystic duct, repeated attacks of acute inflammation produce first distension of the gallbladder and then inflammation and thickening of the involved structures in the area. The distended and inflamed gallbladder comes to lie in close proximity to the common hepatic or common bile duct, and adhesion between the walls of the two structures with compression of the bile duct may produce obstructive jaundice and the type I lesion. The impacted stone may then cause pressure necrosis and further acute inflammation. In time the stone may erode through into the adjacent bile duct, producing the type II lesion or cholecystobiliary fistula The cystic duct becomes obliterated and disappears in the majority of cases, and this fact may create an even larger fistula, with destruction of the anterior wall of the bile duct (type III lesion). As time passes, the stone can slowly migrate into the bile duct, producing a complete necrosis of the duct (type IV lesion). Other internal biliary fistula (cholecystoduodenal, cholecystocolonic or cholecystogastric) have entirely the same mechanism of formation, but they do not form type I lesions as they communicate with organs with a greater lumen than the bile duct.

The practical importance of our new classification is that we propose different procedures according to the stage reached. At operation, it is always important to proceed with great care. Palpation of the impacted stone can give the impression of the presence of external compression of the common bile duct. We prefer to open the gallbladder, extract the stone(s) and visualize the interior of the gallbladder or the common bile duct. An operative cholangiogram should be performed to confirm the diagnosis, determine the location and size of any fistula, detect ductal stones and establish whether there is loss of integrity of the bile duct wall. In none of our cases was a mural defect created accidentally by over-enthusiastic cholecystectomy, a procedure that can produce a large fistula if care is not taken. Partial cholecystectomy helps to define more precisely the extension of any defect[28–30]. If the fistula is small and has eroded less than one-third of the circumference of the common bile duct, the defect can be sutured with fine absorbable sutures and a T tube placed distal to the fistula for 1 or 2 months. If the defect is larger, a cuff of gallbladder is used for fistula closure and a T tube is placed distally. We try never to place the T tube through the fistula, because leakage of bile occurs readily and a benign stricture can appear late after surgery. In some patients who present with stricture of the common bile duct due to this fistula, immediate hepaticojejunostomy may give good late results. End-to-end bile duct anastomosis is inadvisable; all of our six patients in whom we performed this procedure developed a benign stricture early after operation, necessitating hepaticojejunostomy. We therefore insist on preserving a cuff of gallbladder on the bile duct so as to use it in reconstruction. The greatest challenge is posed by the type IV lesions. Complete section of the common hepatic duct may be present and in one of our patients the lesion involved both right and left hepatic ducts. In such cases, we suggest immediate bilioenteric anastomosis or hepaticostomy, leaving a stent or a double T tube in place for a long period. It has been shown in animal experiments as well as in patients[30] that autoreconstruction of the common hepatic duct can occur if a viable longitudinal string of duct is left in continuity. However, we must stress that our follow-up may be too short to assess such cases and that benign stricture can lead insidiously to secondary biliary cirrhosis.

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Wound sepsis following Ramstedt pyloromyotomy

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Wound sepsis is common following pyloromyotomy in children and in a retrospective study of 178 cases the incidence of wound infection was 21 (11·8 per cent). On preliminary analysis, three variables were associated with wound sepsis: age, duration of projectile vomiting and surgical technique. Only surgical technique was found to be statistically significant on sequential multivariate analysis. Mass closure with polydioxanone was associated with a 1 per cent (one of 70) wound sepsis rate. Wound sepsis after pyloromyotomy is dependent on technique, and mass closure with polydioxanone is recommended. The routine use of tension sutures should be abandoned.

Keywords: Pyloromyotomy, wound sepsis, wound closure

Wound sepsis following pyloromyotomy remains a problem with the incidence varying from 0·3 to 14 per cent[1–4]. Immune deficiency, poor nutritional state[1,2] and proximity to the umbilicus[3] have been incriminated, but specific risk factors have not been identified. This study analyses the significance of 14 risk factors for wound sepsis.

Patients and methods

The case records of 192 consecutive pyloromyotomies performed over a 5-year period (1982–86) were reviewed and information on 14 variables collected (*Table 1*) Fourteen patients were excluded, 13 of these had been exposed to antibiotics either in the immediate preoperative period or at the time of surgery, and the medical record was unobtainable in one. Therefore 178 cases formed the study group

In-hospital wound sepsis was diagnosed in the presence of purulent discharge from the operative wound with or without a confirmatory microbiology report.

Operative technique comprised a right upper quadrant incision with rectus transection. Three methods of wound closure were assessed; (A) layered closure with Dexon® (Davis and Geck, Gosport, UK), (B) mass closure with polydioxanone and (C) layered closure with Prolene® (Ethicon Ltd., Edinburgh, UK) to the posterior sheath and catgut to the anterior sheath Nylon 'tension' sutures were used in both techniques A and C.

Skin closure included the use of Dexon, Vicryl® (Ethicon Ltd.) and catgut as subcuticular sutures and Prolene, Ethilon® (Ethicon Ltd) and Nurolon® (Ethicon Ltd.) as interrupted skin sutures. The method of closure was chosen according to the surgeon's preference.

General anaesthesia was used throughout with either suxamethonium, tubocurarine chloride (Duncan Flockhart and Company Ltd , Greenford, UK) or both, or fentanyl as muscle relaxant. Awake intubation was routine and inhalational anaesthetic agents were halothane or isoflurane with nitrous oxide Thiopentone was used in four cases. The period of postoperative nasogastric suction was 24 h.

Statistical method

Non-parametric statistical analyses were performed with the Mann–Whitney U test, and the χ^2 test (with Yates' correction when necessary) was used for comparison of groups of qualitative variables. Factors identified as statistically significant were included in a multiple logistic regression model to assess the simultaneous influence of these variables.

Results

There were 21 (11·8 per cent) wound infections and no wound dehiscences in the 178 cases. Fourteen patients (7·9 per cent) developed minor wound problems, induration with/without erythema, and were categorized as non-infected.

Staphylococcus aureus was cultured from 80 per cent of infected wounds and *Escherichia coli*, *S. albus* and *Proteus mirabilis*, alone or in combination, from the remaining 20 per cent. There were no deaths.

Details of the analysis of the factors that are not related to technique are given in *Tables 2* and *3*. The median age of infants who developed wound sepsis was significantly less (29 days, range 17–64 days) than that of non-infected infants (35 days, range 14–129 days). The duration of projectile vomiting was also significantly different between the two groups, wound sepsis cases vomiting longer (5 days, range 1–7 days) than non-infected cases (3 days, range 1–10 days). The influence of the technique of abdominal wall closure on wound sepsis is shown in *Table 4*. Tension sutures were used in 104 cases, 20 of whom developed wound sepsis (19·2 per cent) compared with one wound infection in cases without tension sutures ($\chi^2 = 11{\cdot}62$, $P < 0{\cdot}001$).

Table 1 *Variables chosen for study in relation to wound sepsis*

Age (days)
Sex
Duration of projectile vomiting (days)
Weight gain from birth
Weight deficit (weight for age on 50th centile, weight on admission)
History of jaundice at birth or subsequently
Breast feeding (>1 week)
Number of 'test feed' examinations
Duration of nasogastric suction in the postoperative period
Method of wound closure
Grade of operating surgeon
Preoperative serum bicarbonate level
Duration of preoperative stay in hospital
Prematurity

Table 2 *Analysis of non-technical factors*

Variable	Wound sepsis		No wound sepsis		*P* value
Weight gain (mg/day)	9·4	(0–40)	10·0	(0–40)	0·102
Weight deficit (kg)	0·61	(0–1·8)	0·65	(0–2·19)	0·814
Number of 'test feed' examinations	3	(2–6)	3	(2–10)	0·591
Duration of postoperative nasogastric suction (h)	24	(1–31)	24	(4–48)	0·732
Preoperative stay (days)	1	(0–6)	2	(0–8)	0·802
Age (days)	29	(17–64)	35	(14–129)	0·01*
Projectile vomiting (days)	5	(1–7)	3	(1–10)	0·005*

Figures given are the median value and range (in brackets). The Mann–Whitney U test has been used for the analysis. *$P < 0{\cdot}05$ indicates statistical significance

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Of 133 wounds closed with subcuticular skin sutures, 14 (10·5 per cent) developed wound sepsis compared with seven (16 per cent) of 45 wounds closed with interrupted non-absorbable sutures. This difference was not significant ($\chi^2 = 0{\cdot}817$, $P > 0{\cdot}5$).

The rank of the operator did not influence the wound sepsis rate (*Table 5*).

Multivariate analysis

Age, duration of projectile vomiting, and technique-related variables (technique A and C *versus* B and subcuticular skin closure *versus* interrupted non-absorbable sutures) were included in a multiple logistic regression model in the first stage of the multivariate analysis. Three variables were entered (age, duration of projectile vomiting and technique A and C *versus B*). Age and duration of vomiting failed to reach statistical significance. Closure technique remained highly significant ($P = 0{\cdot}002$). In the second stage, skin closure technique was introduced and this failed to reach statistical significance. Closure technique continued to remain statistically significant ($P = 0{\cdot}0052$).

Table 3 *Analysis of non-technical variables*

	n	Wound sepsis	%
Preoperative serum bicarbonate			
> 30 mmol/l	52	5	10
25–30 mmol/l	66	9	14
< 25 mmol/l	60	7	12
Sex			
Male	152	18	11·8
Female	26	3	12
Jaundice			
Present	42	5	12
Absent	136	16	11·8
Feeding			
Breast	42	4	10
Bottle	136	17	12·5
Prematurity			
Present	51	3	6
Absent	127	18	14·2

χ^2 test, non-significant for all parameters

Table 4 *Influence of technique of abdominal wall closure on wound sepsis*

Technique of abdominal wall closure	*n*	Wound sepsis	%
A. Layered closure with Dexon	69	14	20
B: Mass closure with polydioxanone	70	1	1
C: Layered closure with Prolene and catgut	39	6	15
Overall	178	21	11·8

$\chi^2 = 12{\cdot}497$, 2 d.f.; $P < 0{\cdot}001$, (A+C) *versus* B

Discussion

The incidence of wound infection following Ramstedt's pyloromyotomy in this study is comparable with wound sepsis rates of 9–14 per cent in other studies[1,2,5–7]. Wound sepsis rates are high in paediatric surgery, ranging from 46·5 per cent in infants to 11·6 per cent in children aged 5 years and over[3]. These high rates contrast markedly with rates of 0·3–4 per cent after Ramstedt's pyloromyotomy reported from North American[4,8–11] and two UK[12,13] series.

The reasons for the differing sepsis rates are not clear and indeed the factors influencing the development of wound sepsis remain ill-defined; immunological and nutritional causes[1,2] as well as proximity to the umbilicus[3] have been incriminated. This study shows that significant factors unrelated to technique include the age of the child and the duration of projectile vomiting before surgery; this implies a compromised nutritional and possibly immunological status not reflected in the body mass.

Before the routine introduction of tension sutures in Aberdeen, layered closure alone was used but was associated with a wound dehiscence rate of 3 per cent[14]. The use of tension sutures was abandoned in favour of mass closure with continuous absorbable monofilament suture (polydioxanone) by one of us (G.G.Y.) in 1984, but continues as the method of choice of some surgeons. We have had no cases of wound dehiscence in the last 5 years either with or without tension sutures and we now believe that tension sutures are not essential in preventing dehiscence. Mass closure with polydioxanone appears effective in preventing dehiscence and in addition is associated with a significantly lower wound infection rate. The use of monofilament absorbable suture material in mass closure has many theoretical attractions as the preferred method of closure in infancy[15]. Although we acknowledge that the development of technique B at the midpoint of the study introduces the possibility of a concurrent artefactual effect, the operative and perioperative management of the entire group remained otherwise entirely consistent, leaving change in technique as the factor contributing to differing sepsis rates.

This study suggests that surgical technique is of prime importance in the avoidance of wound sepsis in the surgery of pyloric stenosis. Although we appreciate the deficiencies of any retrospective study dealing with wound sepsis, the identification of risk factors has hitherto been deficient; a strategy for the use of prophylactic antibiotic can now be asserted based on the risk factors identified as significant.

Acknowledgements

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Table 5 *Influence of grade of operator on wound sepsis*

	Registrar			Registrar + consultant			Consultant		
Technique	*n*	Wound sepsis	%	*n*	Wound sepsis	%	*n*	Wound sepsis	%
A	54	9	17	6	3	50	9	2	22
B	19	1	5	26	0	0	25	0	0
C	23	2	9	3	1	33	13	3	23
Total	96	12	12	35	4	11	47	5	11

χ^2 with Yates' correction, no statistically significant results

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Peptic pyloric stenosis treated by endoscopic balloon dilatation

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Twenty-five patients with proven gastric outlet obstruction secondary to peptic ulcer disease were treated by endoscopic balloon dilatation using 'through the scope' balloons. The stricture could not be negotiated in one patient. Two patients continued to have gastric outlet obstruction despite the dilatation and required surgery. Two patients have returned up to 11 weeks after treatment with signs of recurrent gastric outlet obstruction. Twenty patients (80 per cent) remained asymptomatic (follow-up: median 9 months, range 2–24 months).

Keywords: Gastric outlet obstruction, pyloric stenosis, dilatation

Benign peptic pyloric stenosis has traditionally been treated by surgery[1]. Recently hydrostatic and pneumatic balloons for gastrointestinal strictures have been developed[2,3] and have been shown to be effective in the management of oesophageal strictures. Initial results with pyloric stenosis using wire guided balloon dilators under fluoroscopic control have been encouraging[4] although up to 26 per cent of patients have been found to be unsuitable[5]. Another report quoted encouraging early results in gastric outlet obstruction using the 'through the scope' balloon but information on patient selection was lacking[5]. We describe our 2-year results using balloon dilatation under direct vision.

Patients and methods

Between November 1986 and November 1988, 25 patients (20 men and five women) with benign pyloric stenosis were investigated in the surgical gastroenterology unit. The median age of the patients was 68 years (range 19–86 years). Sixteen (64 per cent) were over 60 years of age and nine had serious associated illnesses. All patients had presented to our surgical unit as emergencies with persistent effortless vomiting. There was, in all patients, a succussion splash indicating gastric outlet obstruction All of the patients had lost weight before admission (*Table 1*) and had a history of dyspepsia. Five patients had hypochloraemic alkalosis and a further ten were clinically and biochemically dehydrated. Gastric dilatation, outlet obstruction and barium retention were confirmed in ten patients using contrast radiography. All patients were treated by rehydration, nasogastric suction and intravenous fluids and were investigated by upper gastrointestinal endoscopy, when the passage of a 9-mm endoscope through the obstruction was found to be impossible. No patient had any evidence of malignancy on endoscopic biopsy of the pyloric region

As these patients were considered to be candidates for surgery, endoscopic dilatation was attempted in the first instance. Dilatations were performed under intravenous sedation using Diazemuls® (Kabi Vitrum Ltd., Uxbridge, UK; median dosage 5 mg, range 2·5–10 mg) and pethidine (median dosage 12·5 mg, range 0–25 mg). A 180 cm polyurethane catheter (TTS® 12 and 15 mm, Microvasive, Milford, Massachusetts, USA) was passed into the lumen of the pylorus and positioned across the stricture. The balloon was then inflated with a 10 ml syringe containing contrast medium and the entire procedure was followed under X-ray control. After the balloon was completely distended it was kept in place for 3 min The procedure was repeated until the stricture was dilated to 15 mm

Results

All patients tolerated the procedure well, experiencing no more apparent discomfort than with a routine endoscopy. Only one stricture proved to be unnegotiable with the balloon. This patient was treated by surgery. In the remaining 24 patients, dilatation was completed such that a 12·8 mm endoscope (Olympus G1F 1T®, Olympus Optical Company, Tokyo, Japan) could be passed into the duodenum with ease. Three of the patients had strictures that were difficult to negotiate with the 'through the scope' balloon and the use of a guide-wire assisted balloon dilatation was required. Of the successfully dilated patients 14 had evidence of active duodenal ulceration. Symptoms of gastric outlet obstruction persisted in two patients for 7 days after treatment. On clinical examination and repeat endoscopy evidence of recurrent gastric outlet obstruction was found and they were treated surgically. Twenty-two patients were discharged home on maintenance doses of H_2 blockers and on a normal diet.

Patients were followed up at 4 weeks and then at intervals of 2 months. All patients underwent repeat endoscopy at 4 weeks but thereafter were only investigated if symptoms or signs of gastric outlet obstruction were present.

Two patients re-presented with symptoms of outlet obstruction at 8 and 12 weeks after dilatation and required surgical intervention. The remaining 20 patients are well and are without endoscopic or clinical evidence of gastric outlet obstruction (follow-up: median 9 months, range 2–24 months). No complications related to the dilatation procedure were encountered in any of the patients studied.

Discussion

Pyloric obstruction has been considered to be an absolute indication for surgery. Classically, the stenosed area is either resected (Polya gastrectomy), reopened (pyloroplasty) or bypassed (gastroenterostomy). Intraoperative dilatation of the pylorus using Hegar dilators at the time of highly selective vagotomy was first described by Johnston *et al.* in 1973[6] with good results. It was therefore suggested that the fibrous stenosis once dilated could be prevented from restenosing if acid output were reduced. Taylor has recently described a pyloric dilating balloon that fits over the endoscope[7], but the prerequisite for this treatment is that the stricture should be wide enough to admit the endoscope. Hogan *et al.*[4] used balloon dilatation under fluoroscopic control and demonstrated improvement in symptoms in 12 patients. Some difficulty in pushing the balloon through the pylorus has been experienced using this technique. Balloons that could pass through the biopsy channel of a therapeutic endoscope ('through the scope' balloons) have recently been developed. In patients with severe deformity of the bulb, passage of the balloon through the stenosis may be difficult or impossible. The more recent

Table 1 *History, symptoms and signs in 25 patients with proven pyloric stenosis*

	Median	Range
Age (years)	68	18–86
Dyspeptic history (years)	3	0 3–10
Duration of present symptoms (days)	10	4–28
Weight loss (kg)	3	2–7
Duration of conservative treatment (days)	6	3–10

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development of a 'through the scope' balloon that has a central lumen allowing the passage of a guide wire has made negotiation of these strictures easier.

The 'through the scope' balloons are manufactured for single use only. However, they may be resterilized by Cidex® (Surgikos, Livingston, UK) immersal for reuse. One of the safety features of this form of balloon is its inherent low compliance. This ensures that the shape of the balloon is maintained despite the inflation pressure produced. These balloons are not durable and are prone to rupture if over inflated. The use of a pressure gauge may be employed to reduce the incidence of such disruption.

The period of dilatation in our series lasted for 3 min and was chosen arbitrarily at the start of the study. Under X-ray screening the contrast filled balloon was monitored carefully. Early experience showed that 'waisting' of the balloon by the stenosed pyloric channel occurred commonly. This 'waisting' resolved within 2 min of the dilatation. We feel that once this 'waisting' has disappeared the radial effect of the dilatation is achieved and prolongation of the procedure time is not necessary.

Our results show that the majority of patients with severe pyloric stenosis can be treated successfully by balloon dilatation with excellent immediate and medium term results. Although bleeding and perforation are potential complications of this technique, they were not encountered in this series. The incidence of restenosis cannot yet be defined but this technique may provide a useful alternative to surgical intervention in poor risk patients.

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Effects of a somatostatin analogue (SMS 201-995) on the growth and development of hepatic tumour derived by intraportal injection of Walker cells in the rat

Administration of a long acting analogue of somatostatin, SMS 201-995 (2 μg subcutaneously twice a day) for 3 weeks after intraportal administration of Walker cells significantly inhibited their growth and development in the liver. This was not due to a direct cytotoxic effect of the analogue on Walker cells whose growth was stimulated in vitro. *Furthermore, SMS 201-995 had no effect on the growth of Walker cells implanted into the thigh of rats suggesting that the inhibitory action of the analogue could be confined to tumour cells growing in the liver. Further studies suggested that the inhibitory effect of SMS 201-995 on the growth of Walker cells in the liver could be related to a marked stimulation of the hepatic reticuloendothelial system, by a reduction in portal venous flow in the early stages of treatment or by a combination of these effects. Further studies are required to delineate more precisely the mechanism whereby SMS 201-995 inhibits the growth of hepatic tumour derived from intraportal administration of Walker cells.*

Keywords: Somatostatin analogue, hepatic tumour growth

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The activity of the fixed component of the hepatic reticuloendothelial system (RES), the Kupffer cells, influences the growth and development of liver metastases. Thus inhibition of hepatic RES activity by gadolinium chloride significantly increases the growth of hepatic metastases in experimental animals[1]. Furthermore, Kupffer cells have been shown actively to phagocytose cancer cells *in vivo*[2]. Consequently stimulation of hepatic RES activity may be of benefit in the treatment of liver metastases.

Growth of hepatic micrometastases is dependent on their blood supply which in the first instance is derived from the portal vein[3]. Therefore splanchnic vasoconstriction which reduces portal venous inflow may also inhibit the early growth and development of liver metastases.

SMS 201-995, a long acting analogue of somatostatin, is a potent stimulator of the hepatic reticuloendothelial system[4] and reduces portal venous flow in rats[5]. Possibly by stimulating hepatic RES activity and reducing portal venous flow, SMS 201-995 may influence the growth and development of a liver tumour. Therefore the purpose of this study was to investigate the effects of SMS 201-995 on the growth and development of experimentally derived hepatic tumour in the rat.

Materials and methods

Percentage hepatic replacement

Forty male Fisher rats (Charles Fisher, UK) weighing between 240 and 310 g were anaesthetized by an intraperitoneal injection of sodium pentobarbitone (6 mg/100 g). Through a midline incision, the portal vein was exposed and 4×10^6 Walker carcinosarcoma cells injected intraportally. The needle was allowed to remain in the portal vein for about 30 s after completion of the injection to avoid spillage of the tumour cells into the peritoneal cavity. Twenty rats received 2 μg SMS 201-995 in a volume of 0 1 ml subcutaneously twice a day for 3 weeks, beginning on the day they were injected with Walker cells. A control group was dosed similarly with the same volume of normal saline. Three weeks later the rats were killed, and the livers were removed, examined macroscopically for the presence of overt tumour and then fixed in formal saline. The percentage hepatic replacement of the liver by tumour was assessed microscopically using the point sampling technique. In brief, this technique involves projecting the microscope slide onto a graph paper screen and counting the number of micrometastases at the intersects.

Hepatic uptake of ^{99m}Tc-sulphur colloid (^{99m}Tc-SC)

Forty-eight rats received 4×10^6 Walker cells intraportally as described above A treatment group ($n=24$) received 2 μg SMS 201-995 twice a day. A control group was similarly dosed with isotonic saline. The control and treated groups were divided into subgroups comprising six rats each and hepatic and splenic RES activity assessed at 24 h and 1, 2 and 3 weeks after intraportal injection of Walker cells All rats were anaesthetized with intraperitoneal sodium pentobarbitone and the femoral vein was cannulated with a 2Fr cannula. Each rat received 2·5 MBq ^{99m}Tc-SC intravenously, and 20 min later the animals were bled, killed and the liver and spleen excised and weighed. The radioactivity in the liver, spleen and blood was counted in a Philips well γ-counter (Pye Unicam Ltd., Cambridge, UK) The activity of the hepatic and splenic RES was expressed in terms of the ratio of liver:blood and spleen:blood ^{99m}Tc-SC.

$$\text{Liver:blood} = \frac{\text{c.p.m./g liver}}{\text{c.p.m./ml blood}}$$

$$\text{Spleen:blood} = \frac{\text{c.p.m./g spleen}}{\text{c.p.m./ml blood}}$$

Hepatic haemodynamics

Forty-eight rats received an intraportal injection of 4×10^6 Walker cells as described previously Twenty-four rats were given 2 μg SMS 201-995 subcutaneously twice a day beginning on the day they were injected with tumour cells. A control group of 24 rats was dosed similarly with the same volume of isotonic saline. Hepatic haemodynamics were investigated at 24 h, 1, 2 and 3 weeks after administration of Walker cells The right femoral artery was cannulated with a 2Fr cannula connected to a pressure transducer for measurement of blood pressure. Through a midline incision the portal vein was mobilized An electromagnetic flow probe connected to a blood flowmeter (Gould, Statham, Model SP2202, Gould Medical Ltd., Lutterworth, UK) was placed around the portal vein cranial to the junction with the pancreaticoduodenal vein. The probe was adjusted to zero after placement on the portal vein by completely occluding the flow.

Splanchnic vascular resistance was calculated using the following formula.

$$\underset{(\text{mmHg min ml}^{-1})}{\text{Splanchnic vascular resistance}} = \frac{\text{Mean arterial blood pressure (mmHg)}}{\text{Portal venous flow (ml min}^{-1})}$$

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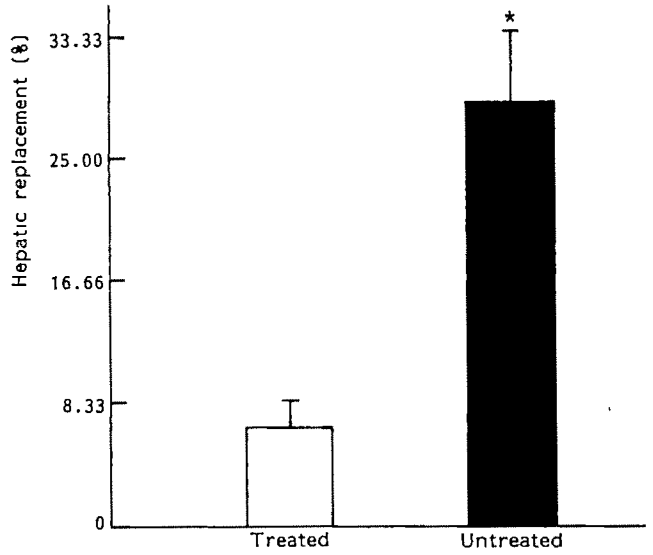

Figure 1 *Percentage hepatic replacement of liver tissue by tumour in control rats (■) and those treated with SMS 201-995 (□) 3 weeks after intraportal administration of Walker cells. The vertical bars represent the s.e.m.*, * P<*0·001 SMS treated* versus *control*

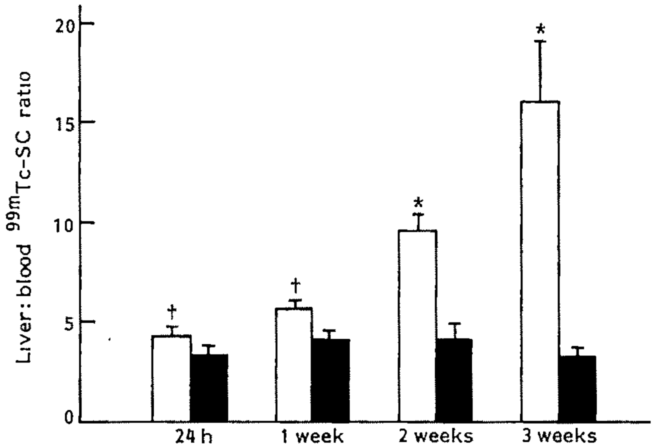

Figure 2 *Alterations in hepatic reticuloendothelial system activity expressed as ratio of liver blood and spleen blood ^{99m}TC-sulphur colloid in rats treated with SMS 201-995 (□) or saline (■) at various times after intraportal administration of Walker cells The vertical bars represent s.e m.*, P⩽*0·01*, † P⩽*0·05 control* versus *SMS 201-995 treated animals*

The effects of SMS 201-995 on the growth and development of Walker cells implanted into the thigh of rats

Twenty rats received an inoculation of 10^8 Walker cells subcutaneously into the right thigh. A treated group ($n = 10$) received 2 μg SMS 201-995 in 0·1 ml subcutaneously twice a day for 2 weeks. A control group was dosed similarly with the same volume of isotonic saline. The animals were then killed and the tumour excised and weighed

The effects of SMS 201-995 on the growth of Walker cells in vitro

Cultures of 10^5 Walker cells were incubated in Williams medium supplemented with fetal calf serum at 37°C in a humidified atmosphere in the presence of 1 μg SMS 201-995 ($n = 10$) or saline ($n = 10$) for 4 days and the cells counted.

Statistical analysis

The statistical significance of any differences between control and treated animals was evaluated using a Student's *t* test for unpaired data

Results

Percentage hepatic replacement

The mean(s.d.) weight of the livers from control animals 15·76(4·31) g was significantly greater than from rats treated with SMS 201-995 (12·04(3·22) g, $P < 0·005$). All control animals had widespread overt liver metastases 3 weeks after administration of the Walker cells. In contrast in the 20 rats treated with SMS 201-995, eight had no obvious tumour and 12 only solitary tumours, the majority of which occurred in the right lobe. The percentage hepatic replacement measured microscopically in the SMS treated rats was significantly less than in the control animals (*Figure 1*)

Hepatic and splenic uptake of ^{99m}Tc-SC

The liver to blood ratios and spleen to blood ratios of ^{99m}Tc-SC activity were significantly greater ($P < 0·01$) in the SMS 201-995 treated animals then in the controls throughout the experiment (*Figures 2* and *3*).

Hepatic haemodynamics

Portal flow was significantly lower ($P < 0·05$) in the SMS treated rats than in the controls 24 h after the start of treatment. Thereafter, no significant difference between control and treated animals was observed (*Figure 4*). Splanchnic vascular resistance was significantly increased in the SMS 201-995 treated animals compared with the controls only during the first 24 h (*Table 1*).

The effect of SMS 201-995 on the growth and development of Walker cells implanted into the thigh of rats

SMS had no significant effect on the growth of Walker cells implanted into the thigh. The mean(s.d.) tumour weights in the control rats were 17·07(9·2) g compared with 20·99(9·5) g in the SMS treated animals ($P > 0·05$).

The effect of SMS 201-995 on the growth of Walker cells in vitro

Addition of SMS 201-995 to the culture medium containing the Walker cells significantly increased their growth (*Figure 5*).

Discussion

The results of this study clearly show that SMS 201-995 significantly reduces the growth and development of hepatic tumour derived from intraportal administration of Walker cells. This is not due to a direct cytotoxic effect of the analogue on Walker cells whose growth is actually stimulated by SMS

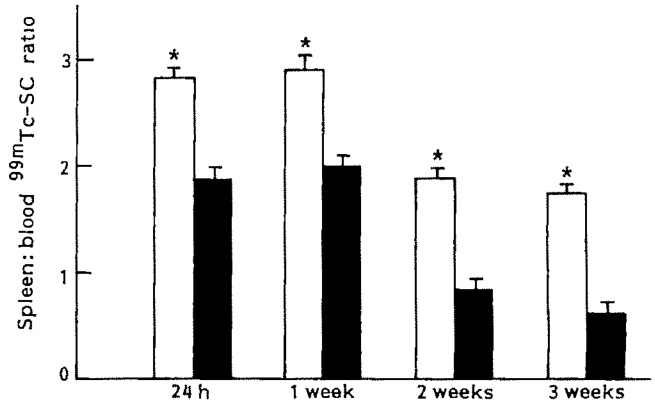

Figure 3 *Alterations in splenic reticuloendothelial system activity expressed as ratio of liver blood and spleen blood ^{99m}TC-sulphur colloid in control rats (■) and animals treated with SMS 201-995 (□) at various times after intraportal injection of Walker cells The vertical bars represent the s.e.m*, * P⩽*0·01 SMS 201-995 treated* versus *control*

Table 1 *Splanchnic vascular resistance in rats treated with SMS 201-995 and control animals 24 h and 1, 2 and 3 weeks after injection of Walker cells*

	Splanchnic vascular resistance (mmHg min ml^{-1})			
	24 h	1 week	2 weeks	3 weeks
SMS 201-995	14·09(1·26)*	10·84(0·69)	7·13(1·23)	6·96(2·26)
Control	9·74(1·47)	10·15(1·61)	9·16(2·80)	6·61(1·40)

Values are mean (s.e.m); * denotes a significant difference between SMS 201-995 treated and control animals ($P < 0·05$), Student's *t* test

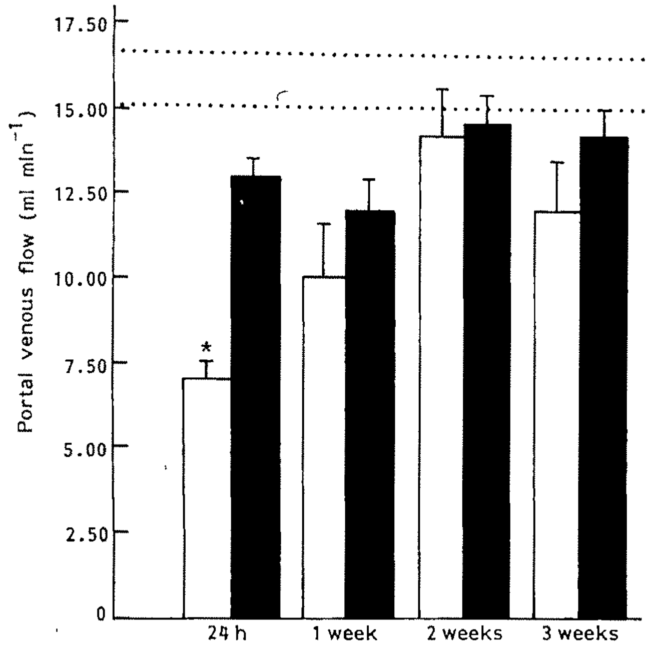

Figure 4 *Portal venous flow in control* (■) *and SMS 201-995 treated* (□) *rats at various times after the administration of Walker cells The vertical bars represent the s.e.m.,* * $P < 0.05$ *SMS 201-995 treated* versus control, *the normal range for portal venous flow in the Fisher rats of the same size and sex is shown by the dotted line*

201-995 *in vitro*. Possibly the inhibition of the growth and development of Walker cells by SMS 201-995 is related to their location within the liver. This suggestion is supported by the observations in this study that SMS 201-995 had no effect on the growth of Walker cells implanted into the thigh of rats. Furthermore it has recently been shown that SMS 201-995 had no significant effect on the development of colonic neoplasia in carcinogen treated rats[6] but produced a regression of neuroendocrine tumours that had metastasized to the liver[7]. Inhibition of the growth and development of hepatic tumour by SMS 201-995 may be due to three possible mechanisms: stimulation of RES activity, reduction in portal venous inflow and inhibition of hepatotrophic factors such as insulin or glucagon.

The RES is an important component of the immunological defence system of the body against malignancy. The fixed component of the RES in the liver, the Kupffer cells, have been shown to phagocytose tumour cells both *in vitro* and *in vivo*[2]. In contrast, inhibition of the hepatic RES by gadolinium chloride enhances the growth of hepatic tumour cells[1]. In the present study, intraportal administration of Walker cells did produce some stimulation of the hepatic RES activity above normal levels but this was probably insufficient to prevent the growth and development of the large number of tumour cells administered. In contrast the hepatic RES of rats treated with SMS 201-995 was markedly elevated throughout the study and this appears to have been sufficient to inhibit the growth of hepatic tumours either completely or partly. This observation is therefore in accord with previous studies which indicated that SMS 201-995 is a potent stimulator of the fixed and circulating components of the RES in experimental animals and in man[8]. Although the activity of the circulating component of the RES was not measured in this study, SMS 201-995 markedly stimulated splenic RES activity throughout the study The precise role of increased splenic RES activity in relation to impairment of the growth and development of hepatic tumour is unknown. However, it may represent a generalized increase in RES activity, including the circulating components, and this overall stimulatory effect on the RES may contribute to the impaired growth and development of hepatic tumour

In the present study, portal venous flow was reduced and splanchnic vascular resistance was increased initially in rats treated with SMS 201-995 compared with control animals.

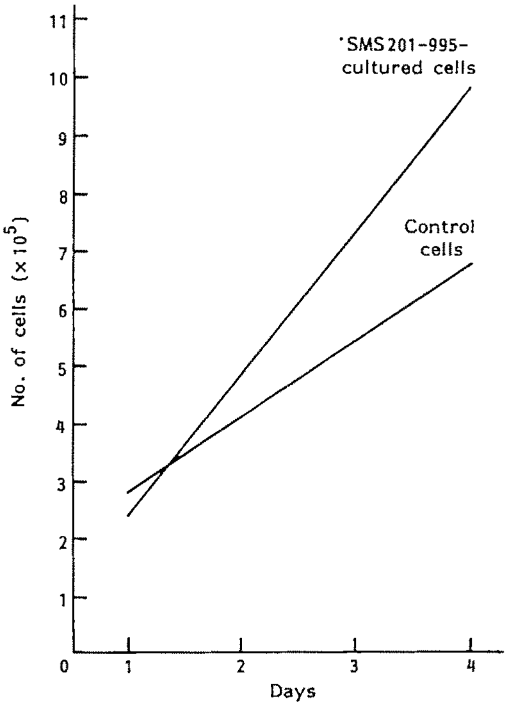

Figure 5 *The effects of SMS 201-995 on the growth of Walker cells incubated* in vitro; *SMS 201-995 treated* versus *control cells*, $P < 0.01$

These observations are consistent with previous reports on the effects of the somatostatin analogue in the cirrhotic rat[5] During their early growth and development, hepatic metastases are dependent on a supply of nutrients from the portal vein[3]. Therefore it is possible that a reduction in portal venous flow elicited by SMS 201-995 in the early stages of development could inhibit the growth of hepatic tumour. After 1 week there was no significant difference in portal venous flow or splanchnic vascular resistance between SMS 201-995 treated and control rats. However, at this stage the hepatic haemodynamics are complicated in the untreated group by the growth of the tumour which could reduce portal venous flow by a mechanical effect Further detailed studies are in progress to evaluate the sequential haemodynamic changes in rats with actively growing tumour and those treated with SMS 201-995.

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Prognostic value of nucleolar organizer regions and ploidy values in advanced colorectal cancer

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The prognostic value of nucleolar organizer regions and ploidy status in patients with Dukes' C colorectal cancer was determined. In addition, nucleolar organizer regions and ploidy status were compared with the established prognostic indices age, sex, tumour location and degree of histological differentiation. Fifty-one patients (27 men, 24 women) aged 35–81 years (median 64·8 years) were studied. Five years after presentation, 16 patients were alive and well. Survivors had significantly lower nucleolar organizer region counts (median value and range) in primary tumours 12 (8–15) and lymph node metastases 11 (8–15) than non-survivors 17 (14–25) and 18 (13–25) respectively ($P<0{\cdot}05$)*. Fewer survivors had aneuploid tumours than non-survivors: four survivors compared with 17 non-survivors. In a regression analysis model, nucleolar organizer regions were the most important individual variable for predicting survival* ($\chi^2=15$, $P<0{\cdot}01$) *while ploidy values* ($\chi^2=6$, $P<0{\cdot}2$) *were equivalent to histological differentiation.*

Keywords: Colorectal cancer, DNA, ploidy, flow cytometry, nucleolar organizer region, nucleolus

Dukes' classification was introduced in 1932 to help predict prognosis in rectal cancer[1]. Although modifications of Dukes' original classification[2–4] and degree of histological differentiation as defined by Broders[5] remain the gold standards for prognosis in colorectal cancer, major anomalies are observed. Indeed the unreliability of these prognostic factors is best illustrated by the fact that although one-third of patients with lymph node metastases at presentation become long-term survivors, approximately one-third of patients with Dukes' B tumours die from their cancer irrespective of histological differentiation[6,7]. Consequently, there is a need for more accurate prognostic indices.

The prognostic value of nucleolar organizer regions and tumour cell DNA content is currently being investigated in a variety of human tumours. Nucleolar organizer regions are loops of ribosomal DNA which occur in nuclei and direct ribosome and protein formation[8]. They are accurately identified by the argyrophilia of their associated proteins. It has been suggested that the numbers of nucleolar organizer regions in nuclei may reflect the state of cellular activity or the malignant potential of that cell[9]. Supporting evidence comes from the fact that different numbers of nucleolar organizer regions have been recorded in benign and malignant melanocytic tumours and in low and high grade lymphomas[8,10]. In addition, nucleolar organizer region counts have been shown to be significantly increased in patients with prostatic tumours who are destined to develop metastases[11].

The measurement of cellular DNA content by flow cytometry is reported to be of prognostic value in a variety of human tumours[12–15]. Changes in cellular DNA content reflect changes in chromosome content and ploidy status[12–15]. Thus tumours can be divided into two groups. those with a normal or near-normal diploid DNA content and those with an abnormal DNA content.

The purpose of this study was to determine the prognostic value of nucleolar organizer regions and ploidy status and to compare them with established prognostic indices in patients with surgically resected advanced colorectal cancer.

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Patients and methods

Patients

Sixty consecutive patients who presented between 1979 and 1982 with advanced colorectal cancer were investigated. Nine patients were eliminated from the study There was inadequate archival tissue for examination in five cases and although the other four patients were alive and well at 1 year they were subsequently lost to follow-up. The remaining 51 patients (27 men and 24 women) aged 35–81 years (median 64·8 years) were studied. All patients had their tumours resected and tumour locations and operative procedures performed are listed in *Table 1*. Histological differentiation and Dukes' classification were determined on routinely processed specimens All patients had Dukes' C tumours and eight patients had clinically apparent liver metastases at presentation. Tumours were classified as well differentiated if greater than half the tumour was gland forming, moderately differentiated if gland formation was noted in 20–50 per cent, and poorly differentiated if more than 80 per cent exhibited a solid growth pattern and/or contained cells with extreme nuclear pleomorphism or a marked increase in nuclear cytoplasmic ratio. Sixteen tumours (31 per cent) were considered well differentiated, 24 were moderately differentiated (47 per cent), nine were poorly differentiated (18 per cent) and two (4 per cent) were predominately mucinous. The fate of all patients is known at 5 years

Nucleolar organizer regions

Sections from primary tumours and lymph node metastases were stained for nucleolar organizer regions in all 51 patients. Tissue sections which had previously been fixed in 10 per cent formalin and embedded in

Table 1 *Tumour location and operative procedures performed*

Tumour location	*n*	Operative procedure	*n*
Caecum	9	Right hemicolectomy or extended right hemicolectomy	19
Ascending colon	6		
Hepatic flexure	2	Transverse colectomy	2
Transverse colon	4	Left hemicolectomy	5
Splenic flexure	1	Sigmoid colectomy	13
Descending colon	4	Anterior resection	6
Sigmoid colon	15	Abdominoperineal resection	6
Rectum	10		

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Table 2 *Nucleolar organizer regions in survivors and non-survivors*

	Primary tumour	Lymph node metastases
Survivors	12 (8–15)*	11 (8–15)*
Non-survivors	17 (14–25)	18 (13–25)

Values are median (range); * $P<0·05$, Mann–Whitney U test

paraffin wax were cut into 4-μm thick sections. These sections were then rehydrated using xylene and graded ethanol solutions. Staining was performed at room temperature for 60 min, using a reaction mixture that comprised 2 per cent gelatin in 1 per cent aqueous formic acid which had been mixed in a proportion of 1:2 volumes with 50 per cent aqueous silver nitrate under darkroom conditions. A 1 per cent methyl green counterstain was applied to each section which was then dehydrated to xylene and mounted.

After staining, representative areas in each section were selected by a pathologist and nucleolar organizer regions were counted by a single observer who was unaware of tumour classification or patient fate. A total of 50 nuclei in each selected area were counted under oil immersion microscopy at a magnification of × 1000 and a median nucleolar organizer region score and a range were calculated. This technique was validated by examining interobserver and intraobserver variations in nucleolar organizer region counts. There were small variations. Two patterns of staining were noted, as previously described[12] Nucleolar organizer regions were visualized as black dots arranged individually (type 1 pattern, simple) or in clusters (type 2 pattern, compound). In type 1 stains, individual nucleolar organizer regions were awarded a score of 1. In type 2 stains, clusters of nucleolar organizer regions were allocated a numerical score according to size by using a graticule in the objective lens. Clusters measuring up to $4 \times 4\,\mu$m were awarded a score of 3, from $4 \times 4\,\mu$m to $6 \times 6\,\mu$m a score of 5 and from $6 \times 6\,\mu$m to $8 \times 6\,\mu$m a score of 7. By this counting technique a single numerical value was obtained for each cell by combining simple and compound nucleolar organizer region scores.

Flow cytometry

A modification of the method developed by Hedley *et al.* to isolate nuclei from formalin-fixed paraffin-embedded tissue was used[16]. Thick sections (50–60 μm) were cut and dried on to glass slides at 50°C for 30 min. Sections were dewaxed in warm xylene for 30 min, placed in cold xylene for 5 min and rehydrated through graded alcohols to distilled water. The tissue was disaggregated with 0·5 per cent pepsin in 0·9 per cent saline with a pH 1·5 for 30 min at 37°C. The digest was centrifuged at 200g for 10 min, washed and then resuspended in 2 ml propidium iodide. After centrifugation and washing, the digest was resuspended in 1 ml of phosphate-buffered saline, syringed three or four times to disaggregate nuclear clumps, and then filtered through a 40-μm nylon mesh. It was not usually necessary to adjust the concentration of nuclei but high concentrations were diluted with phosphate-buffered saline to give approximately 10 nuclei per millilitre. DNA analysis was performed using an FACS 420 flow cytometer (Becton Dickinson, Sunnyvale, California, USA). Red fluorescence (DNA content) was measured between 620 and 740 nm only. The DNA data generated were recorded and stored on floppy disc by an Acorn Archimedes® (Acorn Computers Ltd, UK) computer for subsequent analysis. If possible the fluorescence from 100 000 nuclei was recorded, a minimum of 10 000 nuclei being required to produce interpretable histograms.

The analysis of tissue sections containing normal cells enabled tumour cells with more or less than 2c DNA to be detected. Only histograms with a coefficient of variation of less than eight were accepted. Histograms were classified as aneuploid or diploid and those with a large tetraploid peak were included with the aneuploid group. The detection of tetraploid tumours, especially if they only represent a small fraction of the whole section, is difficult as those tumour cells in G1 have the same DNA content as normal cells in G2 and M. In these cases, a 4c peak representing more than 20 per cent of the whole cell population was designated aneuploid as it is unlikely that normal cells would have such a high G2/M peak. A histogram peak with a shoulder may represent two populations of cells with a small ploidy difference that cannot be resolved from each other but may equally represent technical errors in nuclear preparation or instrument alignment. In these cases analysis was usually repeated and if the shoulder persisted it was considered aneuploid.

Statistics

Correlations between nucleolar organizer region counts and clinical and pathological features (age, sex, tumour location, histological differentiation, and survival time) were examined using the Mann–Whitney U test. Correlations between ploidy values and these features were examined using the χ^2 test The independent significance of individual prognostic variables was determined using Cox's multivariate regression analysis

Results

Five years after presentation 16 patients were alive and well. Of the 35 patients who succumbed, one died as a result of a myocardial infarction and one as a result of a pulmonary embolus. All other deaths were cancer related. The median survival time for non-survivors was approximately 11 months

Nucleolar organizer regions

Nucleolar organizer region counts in survivors and non-survivors are shown as median values and ranges in *Table 2*. Similar counts were detected in both primary tumours and lymph node metastases (*Table 2*). Survivors had significantly lower nucleolar organizer region counts than non-survivors (*Table 2*). Patients with liver metastases had higher counts (20, range 16–22) than patients without liver metastases (16, range 12–21) but the difference was not significant. Higher counts were associated with decreasing histological differentiation with values of 15 (range 12–21) for well-differentiated tumours compared with 17 (range 10–22) for moderately differentiated tumours and 19 (range 16–25) for poorly differentiated tumours but this difference was not significant. There was no correlation between nucleolar organizer region counts and tumour site, age or sex.

Ploidy values

Satisfactory DNA histograms were obtained for primary tumours examined by flow cytometry in 40 patients. Although survivors and patients without liver metastases had a lower percentage of aneuploid tumours the difference was not significant (*Table 3*). Ploidy values did not correlate with degree of histological differentiation with nine out of 14 (64 per cent) well-differentiated tumours, nine out of 20 (45 per cent) moderately differentiated tumours and three out of five (60 per cent) poorly differentiated tumours being aneuploid. There was no correlation between ploidy values and age or sex.

Factors affecting survival

In a regression analysis model nucleolar organizer regions were the most important individual variable for predicting survival ($\chi^2=15$, $P<0·01$) while ploidy values ($\chi^2=6$, $P=0·2$) were as accurate as histological differentiation ($\chi^2=7$, $P=0·2$). Tumour site, age and sex were not of prognostic value.

Discussion

Conventional clinical and pathological indices are unable to predict accurately tumour recurrence or survival time in colorectal cancer. Numerous prognostic factors such as Dukes' classification, modifications of Dukes' classification which take into account depth of penetration and location and number of involved lymph nodes, Broders' histological differentiation, patients' age and sex, tumour location, tumour fixation and carcinoembryonic antigen levels are currently used. It is

Table 3 *Distribution of aneuploid and diploid tumours in survivors and non-survivors and patients with and without liver metastases*

	Aneuploid (n)	Diploid (n)
Survivors	4	6
Non-survivors	17	13
Patients with liver metastases	6	2
Patients without liver metastases	15	17

estimated that at best they accurately predict recurrence in non-metastatic invasive colon cancer in only 50–75 per cent of cases[17]

Prediction of survival is no more precise and 5-year survival rates ranging from 19 to 62·3 per cent according to age, sex and tumour site have been reported[18]. Patients undergoing 'curative resections' defined as removal of all macroscopic tumour have been shown to have a significant survival advantage[19]. Yet it has been demonstrated that a considerable proportion of patients thought to have a Dukes' A, B or C lesion at the time of surgery and believed by the surgeon to have undergone a curative resection have occult hepatic metastases from which they subsequently die[20].

Most of the prognostic indices that are currently used are obtained at the time of tumour resection and subsequently from examination of the resected specimen. Thus they are not available before surgical intervention. Williams *et al.* have shown that preoperative staging of rectal neoplasms could influence subsequent management[21] Using present advances in technology, biochemistry and histopathological techniques they achieved a more accurate staging than hitherto. They concluded that this improved accuracy would alter preoperative and intraoperative decisions, preventing some patients receiving adjuvant therapy as well as selecting patients more accurately for the correct treatment. Consequently prognosis might be improved.

Clearly a number of problems exist. Dukes' classification, modifications of Dukes' classification and the Astler–Coller system of staging are all used, resulting in much confusion[2–4]. Although the TNM system was introduced in order to standardize the pathological staging and make it more comprehensive it has not proved popular[22] This system does give more information about the extent of direct tumour spread and lymph node involvement, as well as taking into account the presence of distant metastases. Other inadequacies of existing staging classifications relate to their failure to take into account local invasion of contiguous tissues and structures, a characteristic which in some studies has been shown to be of greater prognostic significance than involvement of lymph nodes[23,24].

Another difficulty is that morphological features such as depth of invasion and grade rely on the subjective evaluation of the pathologist. Findings may vary enormously as shown by one study dealing with interobserver and intraobserver reproducibility of results[25]. Furthermore, colon cancers have been shown to contain heterogeneous cell populations suggesting that tumours evolve over time with waxing and waning of their cell subpopulations; current prognostic indicators obtained at only one point in time may thus be insufficient for the ongoing management of cancer patients[7].

Initially it was anticipated that assessment of ploidy status by flow cytometry might overcome some or all of these problems. It was reported that 65 per cent of patients with DNA diploid tumours survived 5 years compared with only 7·5 per cent of those with DNA aneuploid tumours[26]. Subsequent investigators have disagreed on the prognostic value of ploidy status. In patients undergoing a 'curative' resection, one study showed that DNA ploidy status was the single most important prognostic factor[27].

Different investigators reported DNA ploidy status to be of individual and independent significance in a multivariate analysis but weaker than Dukes' classification[28,29] Other authors have failed to support these findings, showing instead that although DNA ploidy was of individual prognostic significance it was not of value when included in a regression analysis model[30]. Two other studies found no significant differences in survival between patients with DNA diploid tumours and those with DNA aneuploid tumours[31,32]. In a prospective study of prognostic factors it was found that the surgeons' assessment of operability was the strongest predictor of survival followed by the pathological classification and the patient's age and that DNA ploidy status conferred no independent survival value[6]. In the present study ploidy status was a poor prognostic indicator.

The prognostic value of nucleolar organizer regions has not been previously determined in colorectal cancer. In this study nucleolar organizer regions provided prognostic information over and above that obtained from assessment of haematoxylin and eosin stained sections. Nucleolar organizer regions were the single most reliable prognostic variable for predicting survival. In addition they correlated with decreasing degrees of histological differentiation and with the presence of liver metastases. As for all techniques that could have an application in diagnostic pathology it is important that the method is reproducible in different laboratories and that the reaction can be interpreted with ease. Although evaluation of nucleolar organizer regions is subjective in nature the counting technique used in this study was validated. Interobserver and intraobserver variations in nucleolar organizer region counts were sought and only minor differences were found. Although staining is technically easy to perform and relatively inexpensive, counting nucleolar organizer regions is at present laborious and time consuming.

In conclusion it is unlikely that a single accurate prognostic indicator which can be applied to all cases will emerge in colorectal cancer. In this study the ability of ploidy status to predict survival was disappointing. Considering the varied and contradictory findings of the many investigators who have examined its prognostic value, its potential for future development as a prognostic indicator in colorectal cancer would appear to be limited. In contrast, nucleolar organizer regions would appear to have considerable potential The introduction of a computer program to count nucleolar organizer regions would allow objective evaluation and would allow counting techniques to be standardized thus eliminating variations in nucleolar organizer region scores reported from different laboratories and allowing meaningful comparison of different studies.

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Differential diagnosis of subungual melanoma from a surgical point of view

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Subungual lesions referred to a surgical unit over a 17-year period have been reviewed to assess problems of differential diagnosis and management of suspected subungual melanoma. Such lesions are uncommon, even in a unit with interest in melanoma. Only four melanomas were seen for primary treatment, and eight in all, during the period. We describe the clinical features of other subungual lesions seen in surgical patients which might help in their differentiation from melanoma. Differential diagnosis and a management policy to achieve early diagnosis are discussed in the light of data from this series and study of the relevant literature.

Keywords: Subungual melanoma, differential diagnosis

Subungual melanoma is one of those striking conditions the rarity of which is obscured by the manner in which it catches the imagination of medical author, teacher and student alike. Yet, because of its rarity, it is likely to be misdiagnosed or mismanaged in spite of this universal awareness. It was first described by Boyer[1] in 1854 as a rare tumour. Hutchinson[2], in 1886, called it a melanotic whitlow because it often resembled an infection. Hutchinson described its clinical features from a personal experience of six cases and recognized that injury often drew attention to the lesion and tended to be blamed for its origin. Even now, 100 years later, subungual melanoma is frequently misdiagnosed[3], probably because of its non-specific clinical features and the rarity of the lesion. A review of 5727 malignant skin lesions at the Skin Cancer Unit of the New York University School of Medicine[4] revealed only eight subungual tumours of which only one was a subungual melanoma. Pack and Oropeza[5] described 72 patients with subungual melanoma representing 2·6 per cent of all the melanomas they saw, but this was within a highly specialized referral practice. Other reports have indicated an incidence of from 1·6 to 3·5 per cent[7–9]. In addition there are sporadic reports of subungual melanoma[5,6,10–19] and the published literature indicates a low index of suspicion on the part of clinicians[20,21]. From these reports, it is difficult to determine frequency of subungual melanoma relative to other subungual conditions presenting to surgical clinics.

In view of the difficulty of clinical diagnosis and the consequent problems of management, we have reviewed our own experience with subungual lesions over the past 17 years together with the relevant literature to determine which diagnostic features of different subungual lesions may be confused with melanoma, and to provide a management policy that will lead to an early definitive diagnosis.

The Cardiff experience

The Cardiff experience of subungual lesions is limited and clearly reflects the bias of surgical referral; experience in a dermatology clinic would, doubtless, be different. All subungual lesions, with the exception of haematoma, proved to be rare. Only eight lesions suspicious of melanoma (other than haematoma) were seen in our clinic in a 17-year period. Only four cases of primary referral of subungual melanoma were seen among 445 patients with melanoma from 1972 to 1988. In addition, a further four cases were seen during the same period as secondary referrals after the primary lesion had been excised.

All patients were Caucasians; there were five men and three women. The digits involved were five toes and three fingers. The age of the patients ranged from 53 to 76 years. The clinical appearance of the tumour varied but most of the patients noted a mass below the nail, usually associated with the loss or destruction of the nail (*Figure 1*). Three patients presented with pigmentation and ulceration of the nail bed. Some lesions began as a subungual pigmentation and after several months became ulcerated or painful. History of trauma was available in three patients. The lesion usually failed to heal, became infected and initial diagnosis of pyogenic granuloma was made but biopsy revealed melanoma. Clinically, four of the eight lesions were incorrectly diagnosed. Frozen sections from three patients confirmed malignant lesions but failed to confirm melanoma, which was finally confirmed on paraffin section. These patients were treated by metacarpophalangeal or metatarsophalangeal or interphalangeal amputation. Six of the eight patients underwent lymphadenectomy (axillary or inguinal). Five had therapeutic lymphadenectomy with from two to five nodes positive, while one patient had prophylactic lymphadenectomy (nodes negative). Six of the eight patients died from the disease within 17–50 months. Two patients are alive and well after 48 and 96 months. During the same period, 11 melanomas of a digit were seen which did not involve the finger or toe-nail.

We have never seen a simple subungual naevus, either after referral or as a chance observation. Of the eight primary subungual melanomas reviewed, only one resembled a haematoma (which it did very closely). The very much commoner situation was for a haematoma to be suspected as being a melanoma. The exact number of haematomas suspected to be melanoma seen during this period has not been recorded, but it is estimated at 20 (i.e. haematomas presenting without history of trauma). No cases of eczema or fungal infection of the nail have been referred for surgical opinion to exclude melanoma, although we frequently see these conditions in normal clinical practice. It would appear that melanoma, although rare, is readily misdiagnosed as a fungal infection, but that true fungal infections are recognized accurately by dermatologists and are diagnosed without referral for biopsy.

Clinical features

Subungual melanoma is commonly seen in patients aged 50–70 years. It is equally distributed in men and women, and has a

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Table 1 *Conditions requiring consideration in the differential diagnosis of subungual melanoma*

Subungual haematoma
Paronychia
Pyogenic granuloma
Onychomycosis nigricans
Glomus tumour
Subungual naevus
Subungual exostosis
Mucous cyst
Subungual fibroma
Keratoacanthoma
Bowen's disease
Subungual squamous cell carcinoma

relatively greater frequency in black people than in white people[4,22]. The most common digit to be involved is the thumb and great toe[4].

Symptoms and signs

The majority of the patients present because of the altered appearance of the digit, rather than primarily because of a pigmented lesion. A history of pre-existing pigmented lesions is present in about one-quarter of the cases[4,6] and is frequently attributed to a preceding injury. The common presenting symptoms are pain, discomfort, deformity of the nail, ulceration, swelling and bleeding from the nail bed. Unfortunately, all these represent late disease. These symptoms frequently lead to various forms of medical treatment for 2–3 years before the true nature of the condition is recognized. Subungual melanoma at the usual stage of presentation is recognized with relative ease (*Figure 1*). It then appears as a black, fungating, well demarcated ulcer which has elevated the nail and spread on to the nail fold. Thickening, splitting, distortion or complete destruction of the nail plate may occur, leading to variable degrees of pain, inflammation, pigmentation and discharge. Up to 20 per cent of lesions are amelanotic (*Figure 2*), and are often diagnosed as fungal infections or chronic paronychia. The local nature is important – neither the whole nail nor the whole nail fold is affected. Improvement in outlook is likely only when the condition is diagnosed at a stage when it still resembles a haematoma (*Figure 3*).

Helpful diagnostic features in earlier lesions are bands or streaks of pigmentation in the nail bed, a coal-black border at the edge of the lesion and involvement with pigmentation of the adjacent eponychium. This eponychial pigmentation carries similar diagnostic significance to the narrow rim of superficial spreading change adjacent to a nodular melanoma. Melanoma is likely to have detectable thickness, so that the nail is locally raised. This may or may not occur with haematoma. The 20 per cent of lesions which are amelanotic are particularly likely to be confused with chronic paronychia on clinical grounds.

Although bilateral subungual melanoma has been recorded[3] it normally involves a single digit. The diagnosis must be considered and excluded in any of the following situations: (1) pigmentation of the nail bed; (2) persistent onychia, paronychia or chronic granulation tissue of the nail bed; (3) unexplained splitting, cracking or displacement of the nail bed; and (4) persistence of a lesion following trauma of the nail. In any of these situations, prolonged periods of trial therapy must be avoided, and a definitive diagnosis should be made within 6 weeks. The conditions that require consideration in the differential diagnosis are listed in *Table 1*.

Differential diagnosis of subungual melanoma

Subungual haematoma

Subungual haematoma is typically acute, clearly related to trauma, and sufficiently painful to demand release. Less commonly, this condition appears gradually, painlessly and without a history of trauma. The mechanism of this form of haematoma, which causes the major diagnostic problem in relation to melanoma, is unknown.

Haematomas usually have an irregular outline (*Figure 4*) rather than the straight edge of the melanoma, but they may also have sharply demarcated straight edges (*Figure 5*). They do not usually involve the eponychium or nail fold, as is usual in all except the smallest of melanomas. Stone and Mullins[23] have shown that a haemorrhage in the matrix area is incorporated into the nail plate while the more usual haematoma distal to the lunula remains subcuticular, attached to the nail itself. Hence, when the nail is removed in the case of simple haematoma, the haematoma comes off with the nail as a dried, rather dehydrated, layer attached to its under-surface. In typical examples where it is considered justifiable to observe the lesion, most haematomas will grow along the nail with obvious movement shown over a period of 4–6 weeks, and with a depigmented area appearing in the region of the lunula. However, non-migrating haematomas are sometimes seen. If a melanoma grows along the nail plate in a similar fashion to a haematoma, the lesion will remain obvious in the lunula area and will almost certainly involve the eponychium.

Paronychia

Paronychia is the commonest inflammatory lesion of the nail fold, and acute paronychia causes little diagnostic difficulty. However, chronic paronychia may resemble an amelanotic subungual melanoma to a degree that frequently leads to misdiagnosis. The clinical features are tenderness, redness, purulent discharge and a rapid course with absence of pigmentation. In chronic paronychia the nail fold is swollen and uncomfortable, but the nail itself is not noticeably lifted from the nail bed – even when there is a clear space between the nail fold and the nail plate. The nail is often irregular and yellow or greenish in colour.

Subungual melanoma is predominantly subungual, in contrast to chronic paronychia. On the other hand, an amelanotic melanoma of the nail fold (i.e. not subungual) may resemble chronic paronychia, but will usually spread on to the adjacent skin, well away from the nail fold.

Pyogenic granuloma

This condition may occur in the nail sulcus but does not occur as a specifically subungual lesion. Its features in this region are similar to those elsewhere: a mass of pinkish watery granulation tissue sometimes covered by a crust. The history is rapid: just a few weeks and often follows a minor injury. It is readily diagnosed by biopsy.

Onychomycosis nigricans

This fungal infection of the nail produces a black pigmentation which is easily mistaken for subungual melanoma. It is generally present on more than one nail and often on both limbs, whereas melanoma is usually confined to a single digit. The two lesions can occur together[20] and biopsy should be carried out if a single nail appears atypical.

Glomus tumour

The majority of these tumours occur on the hand and account for 1–2 per cent of all hand tumours[24]. They are characterized by intense, often pulsating, pain which leads to an equally characteristic reaction: patients draw their hand away before the clinician can even attempt to examine it, because the anticipated pain is so intense. The lesion is visible through the nail plate as a small bluish to reddish-blue spot (*Figure 6*). The slow growth and its exquisite sensitivity help to differentiate the glomus tumour from subungual melanoma. When removed, a characteristic bluish-pink lesion resembling granulation tissue is seen (*Figure 7*) and it has usually eroded a depression in the underlying bone of the phalanx, from which it is readily

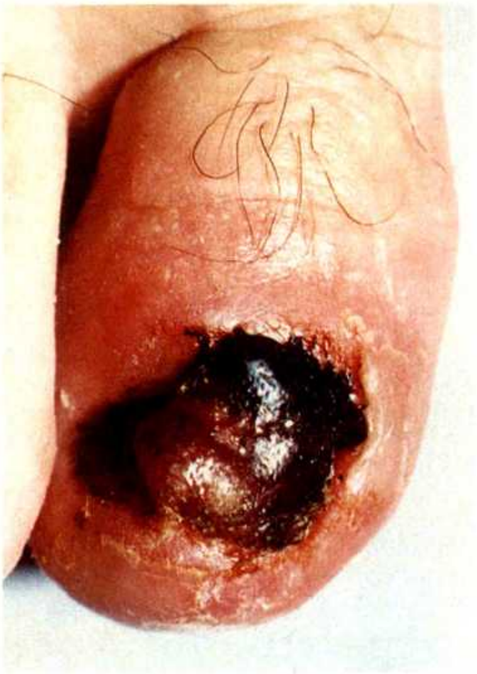

Figure 1 *A typical (late) subungual melanoma, as commonly diagnosed. Note the superficial spreading element extending on the nail fold laterally*

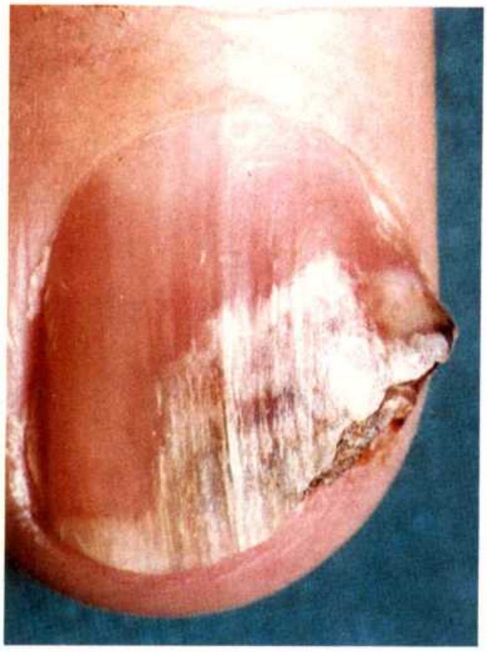

Figure 2 *Amelanotic melanoma. The focality of this lesion suggests a tumour, as most of the nail and nail fold is normal*

curetted. It is not usually necessary to remove the overlying nail matrix.

Benign naevus

Benign naevus is reported as arising in childhood so there is a known long history. It is said to be more common in pigmented races and uncommon in Caucasians. We have not seen a single example, and the only patient referred and thought to have this lesion was followed for 1 year, by which time the lesion had gradually grown out of the nail and therefore appeared to be a reaction to chronic trauma. Many of the lesions illustrated as benign naevi do not seem to have been biopsied. Although said to be common in Negroes and other heavily pigmented races, it is noteworthy that in two surveys of naevi in black races[25,26] no mention is made of subungual naevus. It would seem undoubted that naevoid lesions under the nail in Caucasians are far more likely to be malignant than benign, and it would seem prudent to biopsy any such lesion that might be encountered[27].

Subungual exostosis

This not uncommon condition is most often seen on the great toe. It is particularly frequent in young people and presents as a firm swelling below the nail near the tip. In time it will displace the nail. The triad of pain, nail deformity and radiographic abnormality, together with a clearly defined outline of the lesion, is usually diagnostic. Treatment consists of excision of the excess bone.

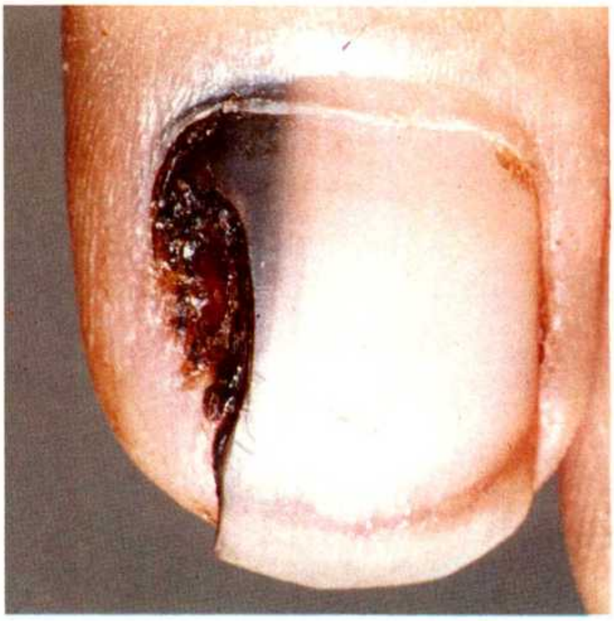

Figure 3 *An earlier (although still fatal) subungual melanoma. Note the straight edge, the involvement of the basal nail fold, and the obvious 'thickness' of the lesion*

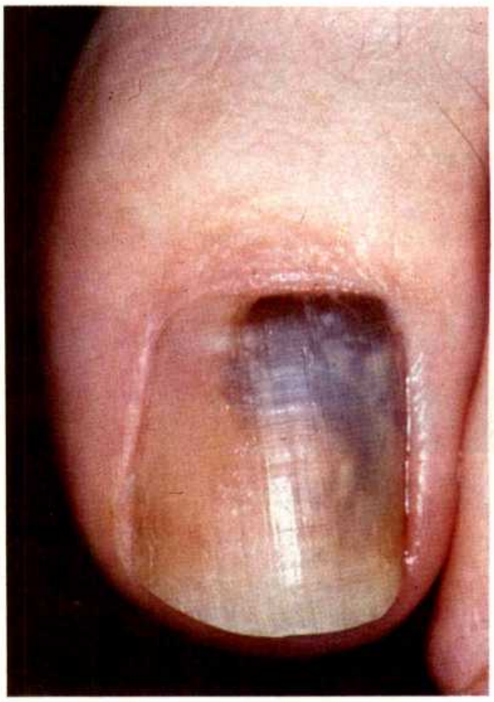

Figure 4 *A painless, subungual haematoma. Note that the nail fold is unaffected*

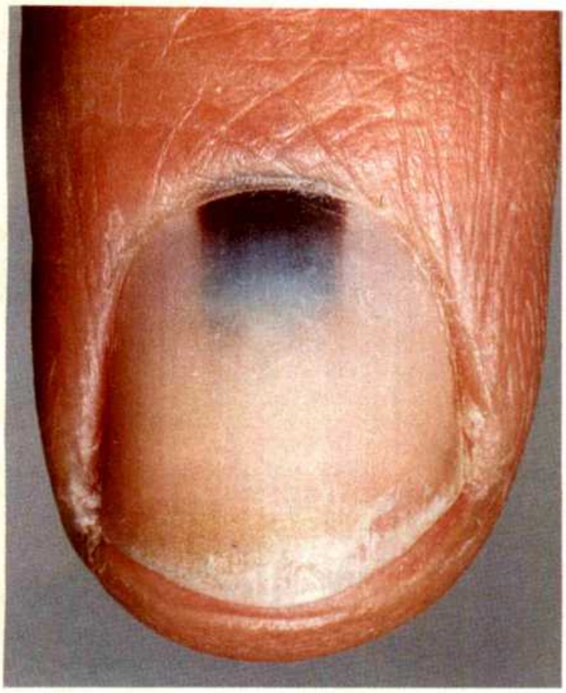

Figure 5 *Painless, spontaneously appearing, subungual haematoma. Note the lack of involvement of the nail fold, which would suggest melanoma* (cf. Figure 3)

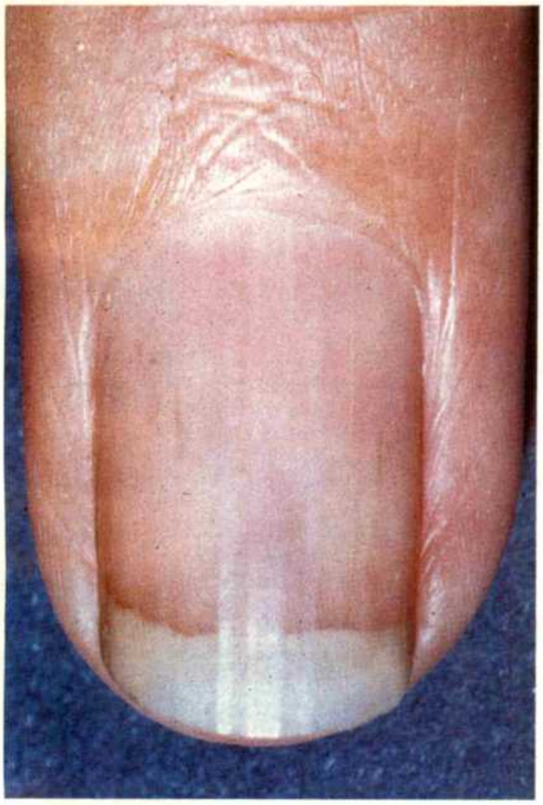

Figure 6 *A subungual glomus tumour seen through the nail, appearing as a bluish tinge beneath the central nail. The vague signs contrast markedly with the extreme symptom of pain*

Mucous cyst

A mucous cyst is not a true tumour but a collagenous degeneration of the extensor tendon of the distal interphalangeal joint. In the past it has been designated as a synovial cyst. The condition forms on the dorsum of the distal phalanx between the distal interphalangeal joint and the base of the nail, from where it tracks down to present as a brown or bluish swelling with distortion of the nail. It is usually quite small, but will eventually deform the nail. It frequently accompanies osteomyelitis of the adjacent joint. As soon as the nail is incised or removed, the colourless, glairy nature of the fluid, typical of that seen in a ganglion, is immediately obvious.

Subungual fibroma

This benign non-pigmented inactive lesion may be single or multiple. Subungual fibromas usually lie outside the nail, projecting from below the cuticle. Occasionally they arise under the nail plate and extend from the base of the nail to its tip.

Keratoacanthoma

Subungual keratoacanthoma is an infrequent, benign, but rapidly growing and aggressive tumour usually situated below the edge of the nail plate or in the distal portion of the nail bed[28]. Diagnosis of this condition depends on the rapid growth with bone destruction and characteristic histology. Its clinical differentiation from squamous cell carcinoma is difficult. Treatment consists of complete excision after removal of the overlying nail.

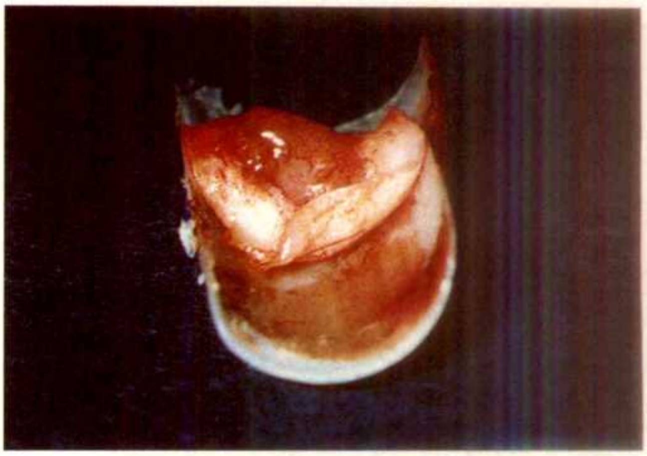

Figure 7 *The glomus tumour from* Figure 6, *lying on the underside of the nail matrix after its removal from a depression in the underlying bone*

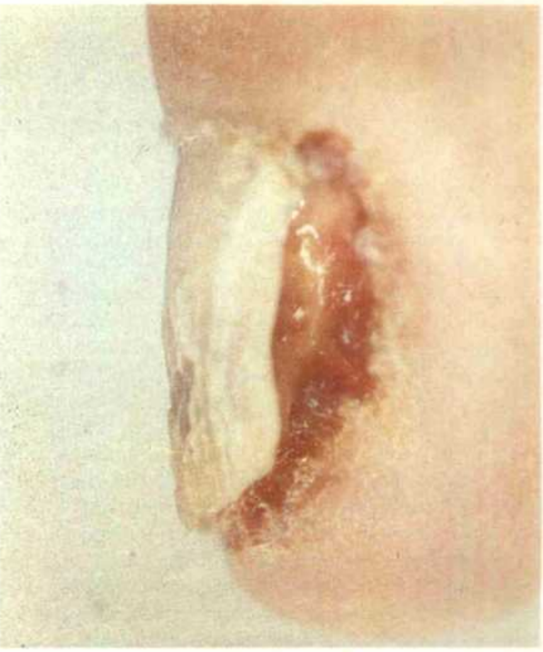

Figure 8 *Squamous cell carcinoma of the nail, treated first as a fungal infection. Histological diagnosis was made only after distal amputation; previous biopsies were reported as benign*

Bowen's disease

Bowen's disease of the nail unit presents as a slowly growing periungual, erythematous, squamous or eroded plaque. Involvement of the proximal nail fold results in the formation of a characteristic whitish band. The fingers are more frequently affected than the toes. The development of Bowen's disease is slow and should be suspected in any case of gradual destruction of a single nail in the absence of fungal infection. Biopsy often reveals invasive squamous cell carcinoma.

Subungual squamous cell carcinoma

This is a tumour of the nail sulcus rather than of the matrix, so it presents from under the distal end or lateral edge of the nail (*Figure 8*). It is such a slow growing tumour that it leads to a sense of false security. A history of 3–4 years is not uncommon[29]. Squamous cell carcinoma ulcerates more quickly than a subungual melanoma but, because it has such slow growth, it bleeds less readily. Complacency about the diagnosis is reinforced by the difficulty of pathological diagnosis. The tumour is frequently so well differentiated that a diagnosis of carcinoma cannot be made on cytological grounds: the pathologist may consider the condition to be pseudoepitheliomatous hyperplasia. It is sometimes necessary to proceed to local amputation on the grounds of presumptive clinical diagnosis supported by a pathological diagnosis of hyperplasia. The prognosis is, in general, good, so that a conservative amputation is often appropriate.

Management policy for cases of suspected subungual melanoma

A lesion that is very likely to be a haematoma

It is reasonable to watch this lesion for a short time, say 4–6 weeks, by which time it should be obvious that the lesion has grown out from the lunula. If this has not occurred, the lesion should be biopsied.

Early lesions that are considered to be naevi or early melanomas

These should be submitted to early biopsy. The easiest way to do this is by drilling a small hole in through the nail with a dental drill. This allows easy and painless access to the lesion to allow a specimen to be taken for cytology. The difference between haematoma and naevoid lesions is easily made on cytological examination, and if this shows abnormal cells it is best to proceed to formal biopsy by removing all or part of the nail.

More advanced lesions, where tissue is available for direct biopsy

Incision biopsy should be used in the first instance, using a gentle technique. We believe this to be less dangerous and less traumatic than removing the nail. If a small incision biopsy confirms the diagnosis of melanoma, one can proceed to appropriate amputation without deep or traumatic biopsy. Early subungual melanoma of a digit is satisfactorily treated by metacarpophalangeal or metatarsophalangeal amputation of the digit, although Papachristou and Fortner[30] suggest extension to the tarsometatarsal level. We advocate this where the nail is elevated or melanoma extends on to the nail fold[31].

We did not have a uniform policy for node dissection during our own, Cardiff experience. The high incidence of nodal deposits with melanoma of the digit would suggest a role for prophylactic node dissection. Therapeutic lymphadenectomy in the absence of systemic disease can be rewarding[32]. The low incidence of *in-transit* metastases from subungual melanoma has led us to reserve limb perfusion with a cytotoxic agent for overt recurrence. It is not possible to give authoritative guidelines on management, because the disease is so rare and no comparative studies of different methods of management have been reported.

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Contralateral inguinal lymph node metastasis in patients with melanoma of the lower extremities

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A retrospective study was carried out on six patients with contralateral inguinal lymph node metastasis from a melanoma of the lower extremity. All six patients were found to have had a previous homolateral groin dissection and in five patients there was intercurrent disease relapse in the leg before or at the same time as the appearance of contralateral node metastasis. Although the prognosis in these patients is unfavourable, two had a survival period of 24 and 32 months and two were still alive 27 months after contralateral groin dissection. In order to determine possible pathways of dissemination, lymphoscintigraphic studies of the leg were performed in another 16 melanoma patients who in the past had undergone a groin dissection. In 13 of them uptake in the contralateral inguinal lymph nodes was detected, indicating that groin dissection can lead to a different lymphatic flow pattern, which is often directed to the contralateral groin. Contralateral lymph node involvement may be an expression of regional disease. In such patients a contralateral groin dissection is advocated.

Keywords: Contralateral inguinal lymph node metastasis, melanoma, lymphoscintigraphy

The clinical presentation of lymphatic spread in patients with a mprimary melanoma of the lower extremity is usually enlarged inguinal nodes on the homolateral side. In the course of the disease, some patients present with contralateral inguinal lymph node involvement. It is unclear whether these contralateral node metastases should be considered to be regional disease and whether locoregional treatment is beneficial.

A subset of patients with contralateral nodal spread after homolateral inguinal block dissection has been studied and the pathways of dissemination have been investigated.

Patients and methods

Patients with contralateral inguinal lymph node involvement

Between 1966 and 1986, of 132 patients treated for regional inguinal lymph node metastasis from melanoma of the lower extremity, six patients were seen with contralateral inguinal lymph node involvement. Three subjects were men and three were women, and their ages ranged from 18 to 69 years (mean 48 years). In two patients the primary tumour site was on the upper leg, in two on the lower leg, and in the other two on the foot. The Breslow thickness of the primary tumour ranged from 1·15 to 4·00 mm (median 2·95 mm). All patients were found to have had a previous homolateral groin dissection and in five patients there had been homolateral lymph node involvement. In all six patients a time interval existed between treatment of the primary tumour and that of the homolateral lymph nodes, varying from 2 weeks to 7 years. Contralateral lymph node involvement became clinically evident 2, 11, 20, 27, 80 and 132 months after homolateral groin dissection. One patient, in whom distant metastases were detected simultaneously with the appearance of contralateral lymph node involvement, received systemic treatment. Of the other five patients, one received radiotherapy to the contralateral nodes and four were treated by contralateral groin dissection. There was intercurrent disease in the leg, consisting of local recurrence and/or *in-transit* metastasis, in five patients, either at the time of homolateral groin dissection or between homolateral and contralateral groin dissection. The follow-up was complete in all patients.

Patients with lymphoscintigraphic evaluation

In order to detect possible pathways of dissemination, lymphoscintigraphic examinations were carried out in another group of 16 melanoma patients who previously had had a homolateral groin dissection. Lymphoscintigraphy of the operated leg was performed 1 year or more after dissection, using a dual head, large field of view γ camera connected to a computer system. Multiple digital images were made 1 h and 4–5 h after subcutaneous interdigital administration of 37 MBq (1 mCi) technetium-99m microcolloid, acquiring counts over 5 min in a 256 × 256 matrix. The scans were evaluated for lymphatic stream patterns in the leg and for uptake in the ilioinguinal and aortic lymph nodes on both sides as well as in the liver.

Results

Patients with contralateral inguinal lymph node involvement

At the time of analysis two patients were still alive, both 27 months after detection of contralateral lymph node involvement. However, both patients had distant metastases. The other four patients had died 4, 5, 24 and 32 months after detection of contralateral lymph node involvement. The two patients who survived for 24 and 32 months, as well as the two who were alive, had been treated with contralateral groin dissection. Disease-free intervals are shown in *Table 1*.

Patients with lymphoscintigraphic evaluation

In 15 of 16 patients in whom lymphoscintigraphic studies were performed no uptake of radioactivity was seen in the operative field. If any isotope activity was detected in the leg, it was observed to be on the medial side. Six patients showed a slow drainage pattern and, in these, isotope activity was seen mainly below the knee. These patients had developed lymphoedema of the leg after groin dissection. In four of these six patients the isotope uptake was clearly seen in the liver. In contrast, only one out of the ten patients with a good drainage pattern showed such a clear uptake in the liver. Medial bypassing of the operative field could not be detected. In nine of the ten patients with a good drainage pattern the operative area was laterally bypassed with filling of the lymph nodes alongside the homolateral common iliac artery and the aorta (*Figure 1*). In nine patients of the latter group, crossing over to the contralateral inguinal lymph nodes by way of a route proximal to the inguinal operative field was detected (*Figure 1*). This pattern of lateral bypassing and crossing over was also seen in four of the six patients with slow drainage.

Discussion

Previous studies of the lymphatic pathways in patients with inguinal lymph node metastases from a melanoma situated on

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Table 1 *Disease-free intervals of six patients with contralateral inguinal lymph node involvement*

Patient No.	Time between primary tumour treatment and homolateral groin dissection (months)	Time between primary tumour treatment and intercurrent limb relapse (months)	Time between homolateral groin dissection and contralateral node metastasis (months)	Time between contralateral node metastasis and haematogenic metastasis (months)
1	0·5	78·5	80·0	16·0
2	84·0	84·0	27·0	9·0
3	1·5	133·5	132·0	11·0
4	7·0	14·0	20·0	27·0
5	2·0	12·0	11·0	4·0
6	1·0	—	2·0	0·0

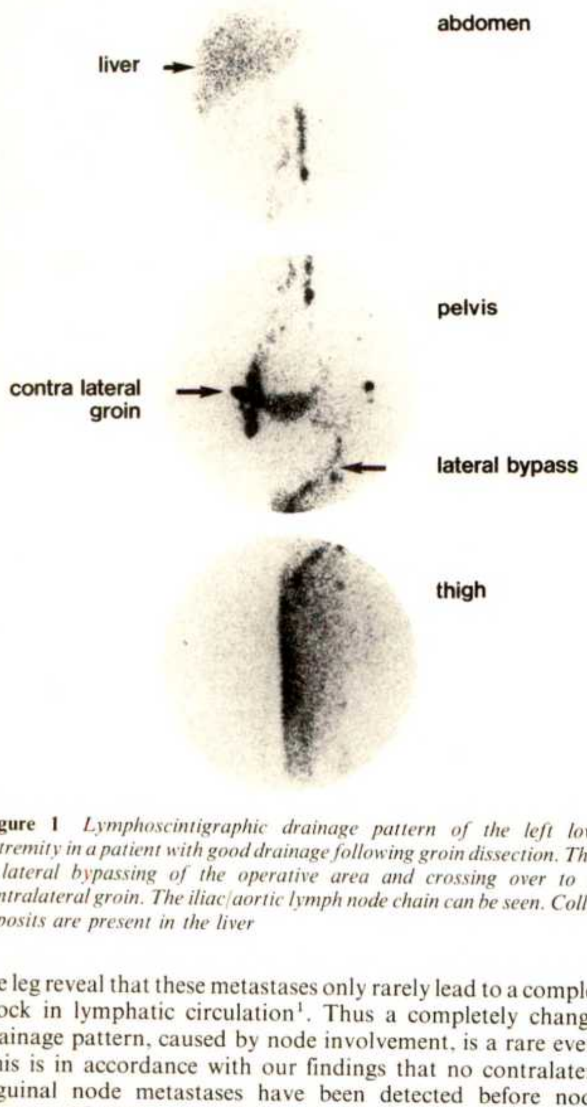

Figure 1 *Lymphoscintigraphic drainage pattern of the left lower extremity in a patient with good drainage following groin dissection. There is lateral bypassing of the operative area and crossing over to the contralateral groin. The iliac/aortic lymph node chain can be seen. Colloid deposits are present in the liver*

the leg reveal that these metastases only rarely lead to a complete block in lymphatic circulation[1]. Thus a completely changed drainage pattern, caused by node involvement, is a rare event. This is in accordance with our findings that no contralateral inguinal node metastases have been detected before nodal surgery. After lymphadenectomy, changing drainage patterns through pre-existing lymphatic connections have been described in patients with a trunk melanoma[2]. Our lymphoscintigraphic studies indicate that the same mechanism probably holds true for the observed crossing over phenomenon after homolateral groin dissection for melanoma of the lower extremity. Therefore, contralateral inguinal lymph node metastasis can result from lymphatic spread.

Remarkably, in our lymphoscintigraphic studies the drainage pathway to the contralateral inguinal lymph nodes was found to be lateral and proximal to the operative field. This pathway is probably subcutaneous, lateral to and proximal to the scar in the groin, and caused by an impaired lymph drainage after resection of the normal medial pathways in the inguinal and iliac/obturator region. The observation that no crossing over took place in two of six patients with slow drainage, compared with no crossing over in only one of ten patients with good drainage, may be explained by the fact that in this group the isotope supply to the groin was not sufficient to produce reliable images of the contralateral lymph nodes.

In our postoperative study an enhanced isotope uptake was seen in the liver of four lymphoedematous patients with slow drainage. An explanation for this finding might be that because of lymphatic obstruction lymphaticovenous shunting had developed, which is in accordance with observations from animal experiments[3].

In our study group of six melanoma patients with contralateral lymph node metastasis, five had an intercurrent limb relapse (local recurrence or in-transit metastasis). In the other patient no intercurrent disease was seen in the leg. The fact that distant metastases in this patient were detected simultaneously with contralateral lymph node metastases suggests that contralateral lymph node metastasis was the result of general dissemination. In the other five patients, distant metastases could not be detected at that time, but in all systemic disease developed later.

In conclusion, patients with contralateral lymph node involvement have a poor prognosis. Nevertheless, the results of our lymphoscintigraphic studies suggest that the disease in these cases may still be regional. In our opinion contralateral radical groin dissection in these patients is to be recommended.

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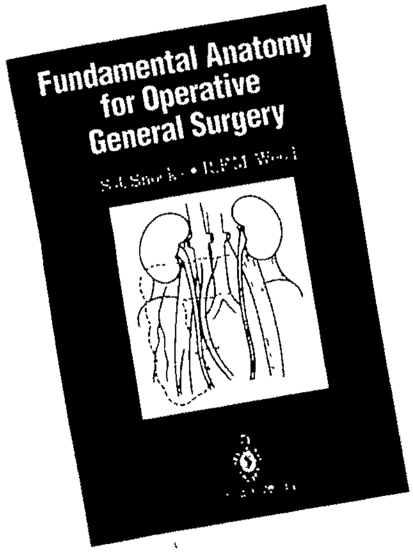

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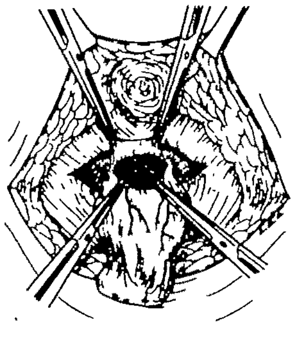

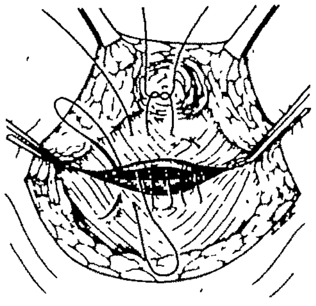

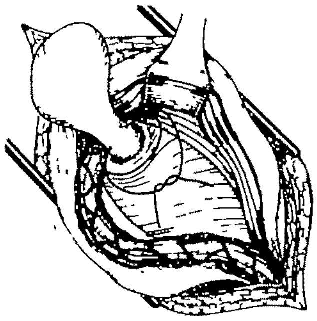

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Long term results of anorectal myectomy for chronic constipation

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Early evaluation of anorectal myectomy in this unit suggested that it might provide clinical benefit to patients with outlet obstruction. Long term results of anorectal myectomy are now available in 63 patients operated on between February 1984 and February 1988 with a median follow-up of 30 months. Spontaneous rectal evacuation without the need for laxatives was recorded in only 11 patients (17 per cent), while 44 (70 per cent) achieved no functional improvement. Mild incontinence developed in 6 patients (10 per cent). Results were independent of preoperative colonic transit or histological evidence of aganglionosis.

Keywords: Constipation, anorectal myectomy, aganglionosis

An increasing number of chronically constipated patients are referred to coloproctologists for investigation and treatment. Two distinct groups of patients have been recognized. those with colonic inertia and those with outlet obstruction. Anorectal myectomy has been proposed as a method of diagnosing short segment Hirschsprung's disease and providing therapeutic benefit for outlet obstruction[1].

The purpose of this report is to record the longer term functional results of anorectomyectomy in a consecutive series of constipated patients.

Patients and methods

Anorectal myectomy was performed in 63 patients between February 1984 and February 1988. All had videoproctographic and electrophysiological evidence of outlet obstruction The mean age was 37·0 years (range 14–70 years) and all except five patients were women. The diagnosis of outlet obstruction was based on the following findings: (1) patients were unable to expel a 100 ml balloon from the rectum; (2) increased electrical activity in the puborectalis during attempted defaecation; (3) an inability to open the anorectal angle and evacuate contrast during the videoproctography. None of the patients had radiological evidence of megarectum but the rectoanal inhibitory reflex was absent in nine patients.

The patients were seen at regular intervals after the operation with a median follow-up of 30 months (range 12–59 months). Results were assessed by frequency of spontaneous defaecation without the use of laxatives, freedom from straining and alleviation of abdominal pain and distension. An overall response was judged as satisfactory, bowels opened regularly without laxatives and no other symptoms; improved, some improvement, but laxatives still required and occasional distension or abdominal pain; poor, no improvement at all

All myectomy specimens were sent for histology, and the presence or absence of ganglion cells determined Twenty-nine patients had anal manometry studies performed by a closed water filled balloon probe before, 3 months and between 12 and 24 months after operation.

Results

Operative morbidity

An intersphincteric abscess developed postoperatively in four patients but in each case the sepsis resolved without functional impairment of continence. Three patients had transient incontinence of flatus after operation and three other patients had persistent minor faecal incontinence.

Functional results

Forty-four patients (70 per cent) obtained no long term benefit from the operation (*Table 1*) and only 11 now consider that rectal evacuation is near normal. Temporary improvement was observed in 31 patients when they were first assessed 8–12 weeks after operation but this was sustained in only 19 when reviewed after 6–12 months. Nineteen patients (30 per cent) later underwent subtotal colectomy because of persistent constipation. There was no correlation between delayed transit time (fewer than 80 per cent of markers passed in 5 days) and outcome of anorectal myectomy (*Table 2*).

Histology

Absence of ganglion cells in the anorectal myectomy specimen 2 cm above the dentate line was found in 12 patients. There was no correlation between aganglionosis and outcome (*Table 3*).

Manometry

The preoperative median (range) resting and squeeze pressures were 129 cmH_2O (87–162 cmH_2O) and 187 cmH_2O (164–339 cmH_2O), at 3 months the values were 106 cmH_2O (69–154 cmH_2O) and 162 cmH_2O (130–354 cmH_2O) and at 12–24 months they were 117 cmH_2O (67–169 cmH_2O) and 177 cmH_2O (139–366 cmH_2O). The only significant change was the transient fall in resting pressure 3 months after operation

Table 1 *Functional results* (n = 63)

Overall	
Satisfactory	11 (17)
Improved	8 (13)
Poor	44 (70)
Bowels opened spontaneously without laxatives	
At least three times per week	14 (22)
Less than three times per week	6 (10)
Laxatives taken	43 (68)
Straining on defaecation	
Absent	6 (10)
Present	57 (90)
Abdominal pain and/or distension	
Absent	16 (25)
Present	47 (75)

Values in parentheses are percentages, median follow-up 30 months

Table 2 *Colonic transit and outcome of anorectal myectomy*

	Normal transit* ($n = 26$)	Delayed transit† ($n = 28$)
Satisfactory	5 (19)	5 (18)
Improved	1 (4)	6 (21)
Poor	20 (77)	17 (61)

Values in parentheses are percentages, * normal transit, >80 per cent of markers passed in 5 days, † delayed transit, <80 per cent of markers passed in 5 days

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Table 3 *Histology and outcome of anorectal myectomy*

	Normal ($n=45$)	Aganglionosis ($n=12$)*
Satisfactory	7 (16)	2 (17)
Improved	5 (11)	3 (25)
Poor	32 (71)	7 (58)

Values in parentheses are percentages; * histology not available in six patients

Discussion

Anorectal myectomy was first described for the diagnosis and treatment of short segment Hirschsprung's disease[2,3]. Later Martelli *et al.*[1] introduced anorectal myectomy as a surgical option for the treatment of idiopathic constipation. Results in patients with anorectal (outlet) obstruction were spectacular: 62 per cent were reported as cured with a further 15 per cent who were improved. These patients had abnormal transit time but there was no videoproctographic or electromyographic assessment.

We reported encouraging results in the first 29 patients of the present series, and 4 months after operation 62 per cent of patients achieved a bowel frequency of at least three stools per week without laxatives[4]. However the assessment only recorded bowel frequency. The results of this long term review demonstrate only a transient improvement associated with a temporary reduction in resting anal canal pressure. This operation is thought to be useful as a method of excluding aganglionosis. An aganglionic segment was found in 12 of 57 cases (21 per cent), similar to the 22·5 per cent reported by Martelli[1]. It has been suggested that the procedure might be most beneficial for patients with short segment Hirschsprung's disease, but our data do not support this theory. Indeed there is some doubt about the clinical entity of short segment Hirschsprung's disease, since the autonomic innervation of the distal anal canal is a variable in normal subjects and there appears to be no correlation between manometry and aganglionosis.

Frequency of defaecation has been used to assess the outcome of operation. However, the presence of abdominal symptoms, the irregular use of laxatives and the emotional instability commonly found in these patients[5] render the number of bowel evacuations an unreliable parameter for evaluation. It would be more appropriate to consider this abnormality as a complex functional bowel disorder apparently unrelated to dietary fibre[6]. Attempts to classify these patients into those with slow colonic transit (colonic inertia) or outlet obstruction, although attractive, has not always proved helpful. The so-called 'paradoxical contraction'[7] of the puborectalis and the disordered flap-valve theory[8,9] have been largely discredited since there has been no therapeutic benefit from division of the puborectalis[10–12]. The high recurrence of abdominal symptoms after subtotal colectomy indicates that colonic transit is not the only physiological disorder in these patients[13]. Failure to demonstrate anatomical or histological evidence of a pelvic floor abnormality in a high proportion of patients suggests that severe constipation is often a psychologically induced functional disorder. The clinical result of this condition is often identified as an inability of the external sphincter and puborectalis to relax during defaecation, currently termed anismus[14]. Attempts have been made to reverse this physiological abnormality by local neuromuscular blockade[15], but the deep-rooted psychological nature of this condition suggests that pharmacological therapy alone may be associated with disappointing results. Bleijenberg and Kuijpers[16] have proposed an interesting treatment for both the physical and mental components of this syndrome.

In view of the risk of mild incontinence in six of 63 patients treated by anorectal myectomy (10 per cent) taken with the disappointing long term results, this operation, even as a diagnostic procedure, can no longer be recommended for chronic constipation.

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Detection of lymph node metastases in colorectal carcinoma before and after fat clearance

One hundred and three colorectal carcinoma specimens were examined to determine the value of the xylene and alcohol fat clearance technique in detecting lymph node metastases. The mesocolon or mesorectum was dissected initially by the traditional method and all the lymph nodes identified were examined histologically. After fat clearance the specimen was dissected again and further lymph nodes were examined. Forty-one specimens were obtained from the rectum and 62 from the colon. Traditional dissection produced a mean of 6·2 lymph nodes per specimen, but following fat clearance a further mean of 12·4 nodes per specimen were found. The total number of lymph nodes recovered varied from two to 69 with a mean of 18·5 per specimen. Traditional dissection showed 45 specimens (43·7 per cent) to have lymph node metastases but after fat clearance a further five specimens (4·8 per cent) were found to be lymph node positive. Therefore, of the 58 specimens graded initially as Dukes' B, five (8·6 per cent) were shown after fat clearance to be Dukes' C tumours. In the Dukes' C cases the mean (s.d.) number of involved lymph nodes per specimen was 2·7 (2·1) by traditional dissection and 4·2 (3·9) after fat clearance. Forty-seven (94·0 per cent) of the Dukes' C tumours were correctly identified after examination of specimens containing up to 13 lymph nodes. Fat clearance of the mesocolon or mesorectum should be used when traditional dissection has failed to identify at least 13 nodes and the tumour has been classified as Dukes' B.

Keywords: Dukes' classification, lymph node metastases, xylene and alcohol fat clearance

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Dukes' classification[1] remains the single most important factor when considering the prognosis in colorectal cancer. In order to classify a tumour accurately many lymph nodes should be examined histologically and the presence or absence of metastases noted. The number of lymph nodes with metastatic deposits[2], and the involvement of the apical nodes, have also been shown to have prognostic significance[3,4]. To determine the effect of adjuvant therapy in colorectal carcinoma it is important to distinguish accurately a Dukes' B from a Dukes' C tumour[5]. Blenkinsopp *et al.*[6] highlighted the wide variation in both the number of lymph nodes identified and the number of lymph nodes shown to contain metastases.

In an attempt to improve the harvest of lymph nodes the technique of fat clearance using xylene and alcohol has been developed[7,8]. Cawthorn *et al.*[8], in a trial of adjuvant preoperative radiotherapy for rectal cancer in Guildford, UK, used this technique. They identified a significantly greater number of nodes in the mesorectum than St. Mark's Hospital and seven other centres in the same study which did not use the clearance technique. Their study also identified a greater number of lymph nodes with metastases in cleared compared with non-cleared specimens.

In contrast, Jass *et al.*[7] found no significant difference in the number of lymph nodes harvested when traditional dissection and fat clearance methods were compared, but the mean time taken for traditional dissection in this study was 23 min. The present study was undertaken to compare the traditional dissection method and the fat clearance technique as applied to the same specimens, with the one technique following the other. An attempt was also made to determine the minimum number of lymph nodes which need to be examined to provide an accurate assessment of the presence of nodal metastases.

Materials and methods

All the specimens of colorectal cancer which were resected over a 1-year period were included in the study. The specimens were from 15 right hemicolectomies, three transverse colectomies, eight left hemicolectomies, 26 sigmoid colectomies, 28 anterior resections and 23 abdominoperineal resections. Most resections were carried out by one surgeon The ligature of the inferior mesenteric vessels was not necessarily 'high' for rectal cancer, but the pararectal dissection was always low and wide[9]

Opened specimens of colon or rectum were received in formalin and allowed to fix overnight. On the following day the mesocolon or mesorectum was dissected from the posterior aspect of the bowel and blocks were taken for histological section from the primary tumour in the normal way The fat of the mesocolon or mesorectum was carefully dissected by routine slicing and a single block was taken from all the lymph nodes found, whether they appeared to be involved by tumour or not. These lymph-node blocks were processed in the normal manner and a count was made of the total number recovered and the number involved by secondary tumour Approximately half of each node was removed and the remainder was left in the specimen

The mesocolon or mesorectum was then placed intact in a bath of alcohol (100 per cent) and kept there for approximately 1 week, the alcohol was changed every day during this period. The specimen was then placed in neat xylene and left there for approximately 2–3 weeks with several changes of xylene during this time Three weeks later the specimen was examined to see whether the fat had cleared, and if it had not it was placed in xylene for a further week. A fully cleared specimen could be examined in a fume cupboard using back lighting Any lymph nodes found, which had not previously been sampled, were taken for histological examination. It was possible to identify previously sampled nodes because these had been cut through at the first examination. A count was then made of the additional number of lymph nodes recovered at the second examination. A single block was again taken from each node and examined histologically for the presence of tumour deposits.

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Tumours in the Dukes' C category were not subdivided into C_1 and C_2 in this study.

Results

One hundred and three specimens of colorectal carcinoma were examined. The sites of the tumours and the mean numbers of lymph nodes found by traditional dissection followed by fat clearance are shown in *Table 1*. The total number of lymph nodes recovered, irrespective of whether they were involved by tumour or not, ranged from two to 69 with a mean value of 18·5 per specimen. The distribution pattern is shown in *Figure 1*. The median value was 16·6 for the 103 cases examined and 16·8 for the 41 rectal cases. The mode for the 103 cases was 13·0 and that for the 41 rectal cases was 12·4. A small number of specimens had a very large number of nodes (more than 45 per specimen). The mean number of nodes found in specimens from the upper rectum was 23, compared with 18 from the midrectum and 15 from the lower rectum.

Forty-five specimens (43·7 per cent) were found to have lymph node metastases by the traditional dissection method. After fat clearance five further specimens (4·8 per cent) were found to have node involvement making a total number of 50 Dukes' C cases (48·5 per cent). Of these five tumours, one was located in the right colon, two in the descending colon and two in the rectum.

The mean (s.d.) number of involved lymph nodes identified by traditional dissection in Dukes' C specimens was 2·7 (2·1) but this increased to 4·2 (3·9) when nodes identified by fat clearance were included. The presence of an increased number of involved nodes was found in 24 specimens. The comparable figures for Dukes' C specimens from the rectum only were 2·7 (2·1) and 4·8 (4·6).

In order to determine the minimum number of lymph nodes which require to be examined histologically to provide an accurate estimate of the presence or absence of metastases, the 50 Dukes' C cases were considered separately. As the total number of lymph nodes examined increased, the cumulative percentage of specimens with nodal metastases also increased (*Figure 2*). Twenty-six (52 per cent) of the Dukes' C tumours were identified by the examination of specimens containing up to six lymph nodes A further 21 Dukes' C tumours were identified by examination of the specimens which contained between seven and 13 lymph nodes; therefore, 47 (94 per cent) of the C tumours were identified after examination of the specimens in which up to 13 lymph nodes were found. The remaining three tumours in the C group were found in specimens which had 15, 18 and 21 lymph nodes respectively.

Discussion

Previous studies using the xylene and alcohol fat clearance technique[7,8] have been applied to rectal tumours. In this study all colorectal cancers were included but there was no difference in the effects of fat clearance when comparing varying primary tumour sites. Fat clearance yielded increased numbers of lymph nodes, from all specimens, when compared with traditional dissection. Cawthorn *et al.*[8] identified a mean number of 23·1 nodes per specimen in the mesorectum of patients with rectal primary tumours, using the fat clearance technique. They compared this with 13·1 nodes identified by the prolonged traditional dissection at St. Mark's Hospital and 10·5 nodes found at seven other 'non-cleared' centres, concluding that the clearance technique identified a greater number of nodes in the mesorectum. In this study an average of 6·1 nodes per specimen were identified by traditional dissection in the mesorectum of the 41 cases of rectal carcinoma, but following fat clearance a total of 18·9 nodes per specimen were found. This study therefore supports the findings of Cawthorn *et al.*[8] that the fat clearance technique is of use in increasing the yield of lymph nodes from the mesorectum rather than the conclusions of Jass *et al.*[7] who found no significant difference between the two techniques. Further the increased yield of lymph nodes applied to specimens from all areas of the colon. This study shows that different individuals have a widely different number of nodes, irrespective of whether they are involved by secondary tumour or not.

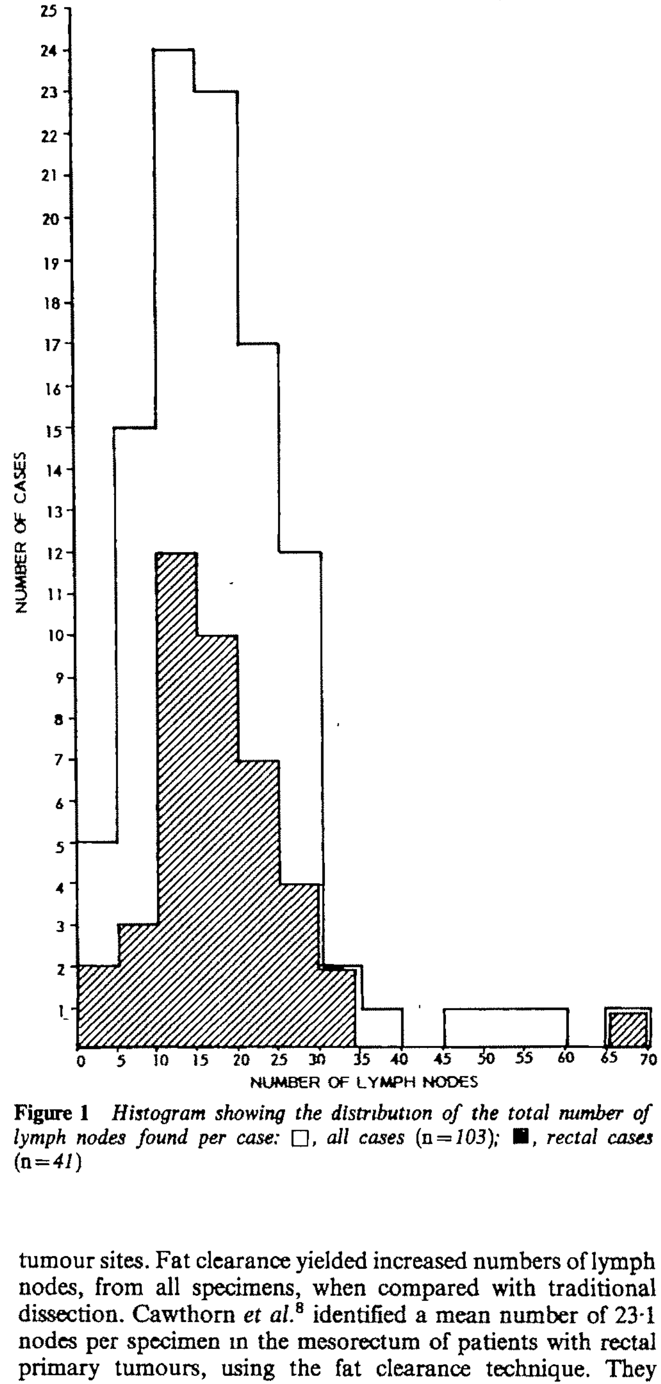

Figure 1 *Histogram showing the distribution of the total number of lymph nodes found per case:* □, *all cases* (n = *103*); ■, *rectal cases* (n = *41*)

Table 1 *Site of primary tumours and numbers of lymph nodes identified by both techniques*

Tumour site	Number of cases	Number of lymph nodes identified*		
		Traditional dissection	Fat clearance	Total
Right colon	15	9 6 (8·8)	11 3 (7·1)	20 9 (13·4)
Transverse colon	3	4 3 (1·5)	6·3 (9·3)	10·9 (9 3)
Left colon	8	4·5 (2·2)	13·4 (7·3)	17·9 (9·1)
Sigmoid colon	26	5 2 (4·5)	13 2 (8·4)	18 5 (10·2)
Rectosigmoid	10	5 4 (3·1)	11 4 (7 2)	16 7 (8 5)
Rectum	41	6·1 (4·3)	12·7 (8·1)	18·9 (10·9)
Total	103	6 2 (5·1)	12 4 (7·9)	18 5 (10 7)

* Mean (s.d.)

The increase in number of Dukes' C cases from 43·7 to 48·5 per cent following fat clearance is in agreement with Cawthorn *et al.*[8], who found 53 per cent of C tumours in fat cleared specimens compared with 50 and 48 per cent in the two

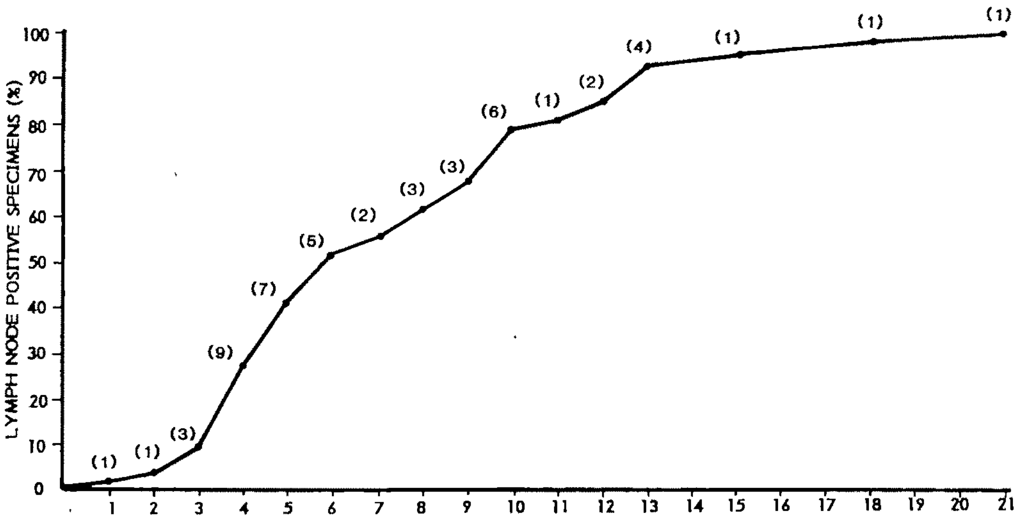

Figure 2 *The total number of lymph nodes recovered from each specimen compared with the cumulative percentage of specimens which had lymph node metastases. The figures in parentheses are the actual number of specimens which yielded the given number of lymph nodes*

'non-cleared' groups. They concluded that this was not a significant difference and the same is true of the present series. However when only the Dukes' B tumours are considered 8·6 per cent were incorrectly classified before fat clearance examination. The number of lymph node metastases found in the present study could still be an underestimate as Wilkinson and Hause[10] have shown that taking several blocks, rather than just one, from any one node can reveal an increased number of nodal metastases. The two stage technique, on one specimen, used in this study produced similar results to that of Cawthorn *et al*[8] who applied the two techniques to different specimens and compared the results from the different groups.

In addition to demonstrating an increase in the number of specimens which have nodal metastases following fat clearance, this study has also confirmed that in Dukes' C specimens fat clearance yields an increased number of nodes which contain metastases. Fat clearance therefore gives a more accurate estimate of the amount of tumour bulk contained in any given specimen of mesocolon or mesorectum.

This study has also established that the more lymph nodes which are examined the more accurate the detection of metastatic deposits. Obviously by the time all the nodes in a specimen have been examined staging can be made with complete accuracy, but there has been long debate on the minimum number of nodes which require to be examined to give a realistic assessment. From the present study it appears that if at least 13 lymph nodes are examined histologically then more than 90 per cent of the specimens which contain nodal metastases will be identified. As the fat clearance technique is unpleasant and time consuming, it is reasonable to suggest that all specimens of mesocolon or mesorectum initially reported as showing no nodal metastases after traditional dissection should undergo fat clearance and further examination if less than 13 lymph nodes were originally recovered.

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Function after ileal pouch and stapled pouch–anal anastomosis for ulcerative colitis

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Fourteen patients with ulcerative colitis underwent formation of an S ileal pouch and construction of a stapled pouch–anal anastomosis by a modified technique, which eliminated the use of purse-string sutures. Eleven have had their covering ileostomies closed. Anal manometry performed before and a median of 9 months after ileostomy closure showed significant impairment of internal anal sphincter function. Night evacuation was significantly reduced in the stapled group compared with a similar group of patients who had undergone S ileal pouch formation, mucosal proctectomy and manual transanal anastomosis, but this was the only parameter of function to show a difference. A stapled pouch–anal anastomosis may be superior to the conventional procedure but it still may lead to internal anal sphincter damage which cannot be due to mucosectomy or prolonged anal retraction.

Keywords: Pelvic ileal pouch, anal manometry, bowel function, stapled anastomosis

The operation of mucosal proctectomy and pelvic ileal pouch formation has rapidly become an established technique for the surgical treatment of ulcerative colitis and familial adenomatous polyposis[1]. Indeed in most centres which specialize in coloproctology, the operation is now the procedure of first choice for most patients with ulcerative colitis. Despite the success of the procedure, there remain certain problems. The operation is technically demanding and requires a considerable learning period. Although most patients are continent for most of the time, many leak both mucus and faeces intermittently and particularly at night. The average number of bowel actions gradually decreases in time, but in most series six per 24 h seems to be the norm[2]. Some patients also complain of urgency of defaecation similar to that experienced while they had their disease. These defects in bowel function may in part be explained by the damage inflicted on the internal anal sphincter[3–5]. It is widely believed that this damage is caused by the mucosectomy itself together with the wide anal retraction required to achieve it. In order to simplify the technique and prevent damage to the internal anal sphincter we, like others[6,7], have used a stapling technique to effect the pouch–anal anastomosis. By eliminating the mucosectomy and the consequent anal retraction we hoped to prevent damage to the internal anal sphincter which occurs during the conventional operation. In order to simplify the stapled pouch–anal anastomosis we have modified our technique to eliminate the need for purse-string sutures[8].

Patients and methods

The operative technique (Figures 1 and 2)

Colectomy (if not performed previously), mobilization of small intestine and perimuscular dissection of the rectum were performed in an identical manner to the conventional operation[9], but the dissection of the rectum was continued down to the pelvic floor. Division of the anococcygeal attachment allowed the rectum to be lifted forwards between the two levator ani muscles. The rectum was strongly retracted upwards and a transverse stapling instrument was applied across the lower rectum at the level of the levator ani muscles. The new Roticulator 30® stapler (US Surgical Corporation and Auto Suture UK, Ascot, UK) was ideal for this manoeuvre because of its flexible head which could be angled on the instrument's shaft. Before the stapler was fired, the perineal assistant placed his index finger in the anorectum to determine the length of anorectum remaining. In most patients the proposed level of transection was found to be 1–2 cm above the dentate line. The stapler was fired and a right angled clamp was placed approximately 1 cm above it, the rectum was excised in the usual way.

A triplicated ileal pouch was then constructed from the terminal ileum using 15-cm limbs but with no efferent spout. The pouch was constructed in two layers using manual sutures but leaving the middle part of the anterior suture line unfinished for the later insertion of the EEA® anvil (US Surgical Corporation and Auto Suture UK). The anastomosis was effected without using purse-string sutures and this was most readily accomplished by using the Premium CEEA® (US Surgical Corporation and Auto Suture UK), although the conventional EEA was also used in some patients.

The cross-stapled top of the anal canal was pierced by the trocar point attached to the instrument shaft, while the anvil piece was taken separately and inserted into the lumen of the pouch through the unfinished anterior suture line. The latter was guided to the base of the pouch which was punctured by the pointed end of the anvil shaft well away from the suture lines. The trocar was then removed and the anvil shaft was pushed into the main instrument shaft to connect the gun, the gun was approximated and fired, establishing the anastomosis. A covering loop ileostomy was constructed in the usual way.

Patients

Between 1987 and 1988, 14 patients with ulcerative colitis underwent this procedure, nine of whom had previously had their colon excised. Eleven patients had their ileostomies closed and were available for study: there were six men and five women of median age 31 years (range 17–53 years).

Anal manometry was performed, using standard balloon manometry with a station pull through technique[10], in ten patients before the operation and at a median of 9 months (range 1–14 months) after the operation. Eight patients were studied between 6 and 14 months after ileostomy closure but two were studied at 1 and 3 months respectively. Of these two, one patient had his pouch removed because of continued pelvic sepsis and the other refused further investigation. Maximum basal anal pressure and maximum achieved pressure were measured. Maximum squeeze pressure was calculated as the maximum squeeze increment found on subtraction of basal pressures from achieved pressures.

Ten of the 11 patients were assessed clinically at 12 months after ileostomy closure. The patient who had his pouch removed was assessed at 1 month. Assessment was by a detailed clinical questionnaire completed by the interviewer, who was a surgeon who had not personally been involved in the patients' care. Questions that related to the patients' postoperative bowel function included day and night frequency, the degree of difficulty in evacuation, feeling of incomplete evacuation, continence, use of constipating drugs and the overall effect of the operation on the patients' social activities.

The clinical results were compared with 12 patients who had previously undergone mucosal proctectomy and ileal S pouch–anal

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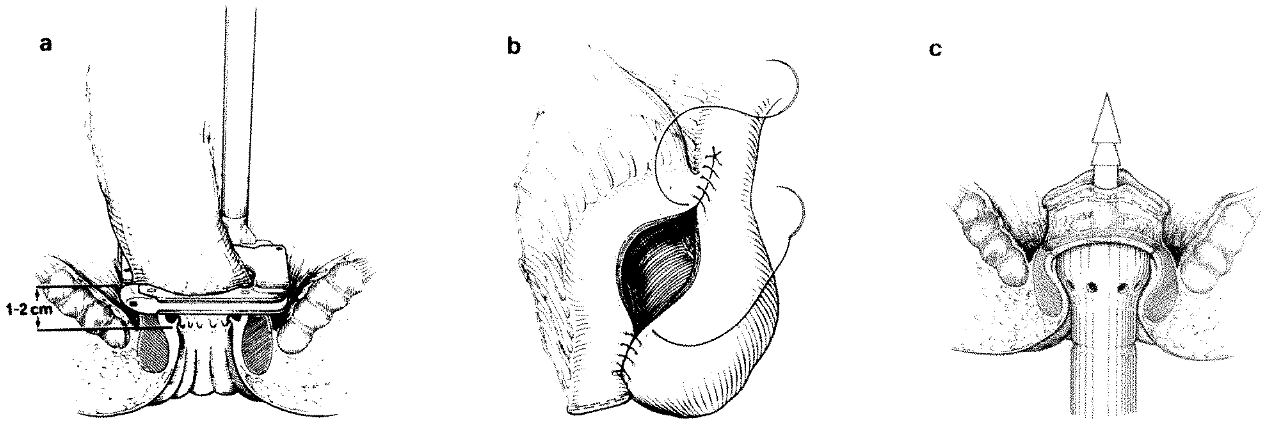

Figure 1 *The operative technique:* **a** *rectal transection at the level of the pelvic floor using the Roticulator 30 stapler;* **b** *S pouch formation leaving a defect in the anterior suture line;* **c** *the stapled top of the anal canal is pierced by the trocar of the Premium CEEA*

anastomosis by the standard manual technique. The two groups were similar with regard to age and sex distribution but the median time since operation was 6 months in the transanal group.

Statistical analysis

The Mann–Whitney *U* test was used to compare preoperative and postoperative basal and squeeze pressures. The χ^2 test with Yates' correction was used to analyse the significance of the difference in function between the patients with stapled and manual anastomoses.

Results

Morbidity and mortality

There was no mortality. The morbidity for all the 14 patients who underwent a stapled pouch–anal anastomosis is listed in *Table 1*.

Manometry

The mean (range) maximum basal anal pressure was 75 cmH_2O (52–110 cmH_2O) preoperatively; this decreased significantly to 34 cmH_2O (20–60 cmH_2O) postoperatively ($P<0{\cdot}01$; *Figure 3*).

The mean (range) maximum squeeze pressure was 140 cmH_2O (26–350 cmH_2O) preoperatively; this decreased to 93 cmH_2O (14–190 cmH_2O) postoperatively (n.s.; *Figure 4*).

Exclusion of the results of the two patients who were studied at 1 and 3 months after ileostomy closure did not change the statistical differences.

Clinical function

Stapled pouch–anal anastomosis (*Table 2*). Seven patients (64 per cent) had perfect continence, two patients (18 per cent) experienced occasional night leakage, once a week or less, one

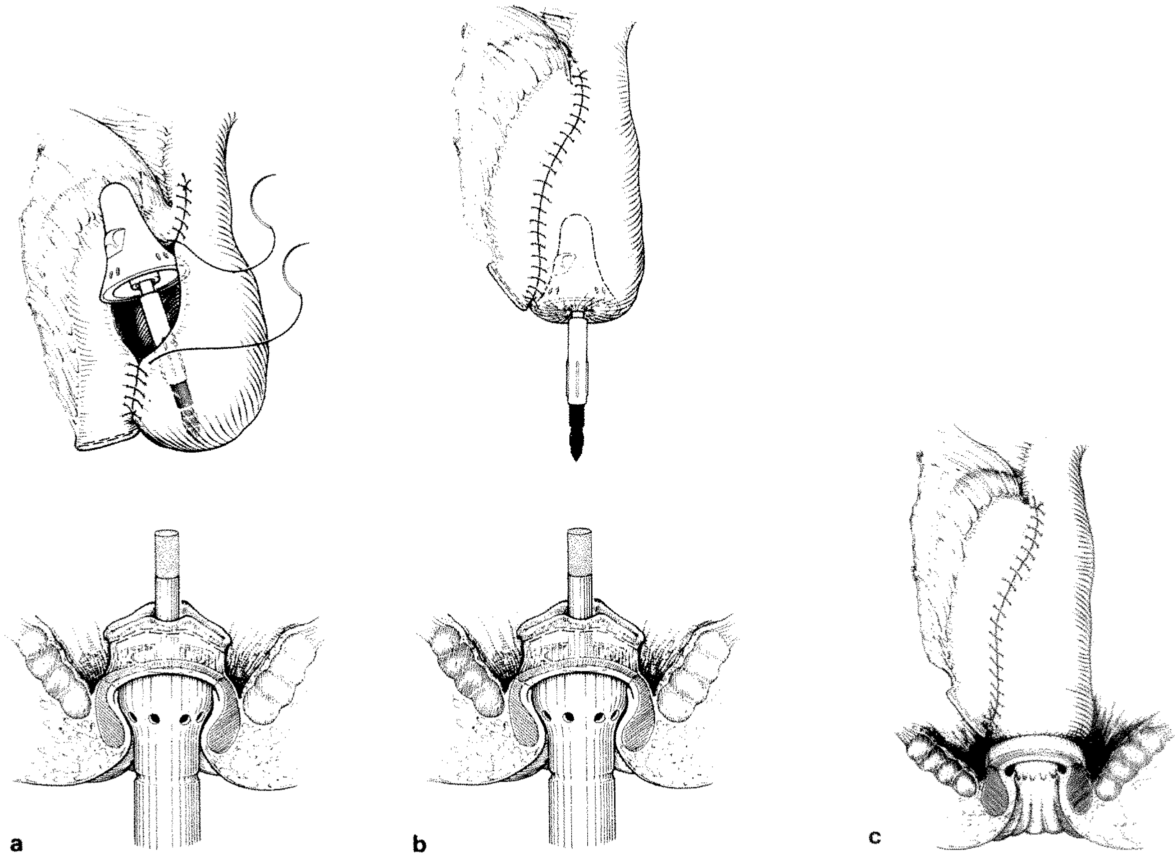

Figure 2 **a** *the anvil is inserted into the pouch through the unfinished anterior suture line and pushed through the base of the pouch and the trocar is removed from the instrument;* **b** *the anvil is pushed into the Premium CEEA gun shaft after the anterior suture line of the pouch has been completed;* **c** *the anastomosis is completed after firing the Premium CEEA and the gun is withdrawn*

Table 1 *Morbidity and mortality in stapled pouch–anal anastomosis*

	n
No. of patients	14*
Mortality	0
Morbidity‡	
Major pelvic sepsis	2†
Pouch–vaginal fistula	2
Postoperative pancreatitis	1
Stricture needing repeated dilatation	2
Wound infection	1
Acute pouch dilatation	1

*11 had ileostomy closed; †1 required removal of the pouch; ‡5 patients affected *in toto*

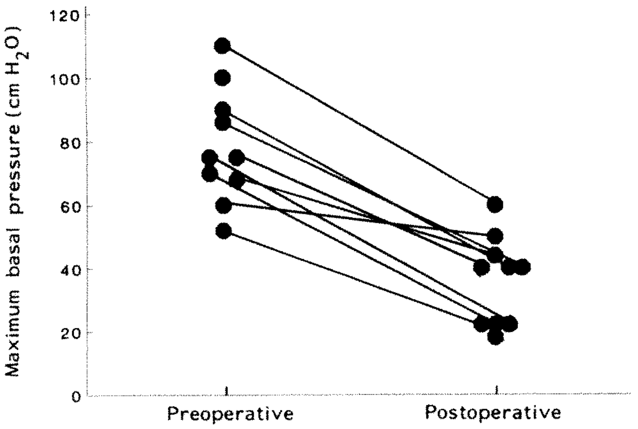

Figure 3 *Maximal basal anal canal pressure before and after stapled pouch–anal anastomosis. The postoperative values are significantly different from the preoperative values* ($P<0.01$)

patient (9 per cent) leaked small quantities every night and one patient (9 per cent) had major faecal leakage day and night. The median number of bowel actions during the day was six (range 2–15); the median number of nocturnal bowel actions was 1 (range 0–5), but only five of the 11 patients (45 per cent) had any night evacuations. Nine patients (82 per cent) had spontaneous evacuation, the remaining two patients (18 per cent) could evacuate spontaneously but, because they emptied their pouches incompletely, they were advised to intubate their pouches regularly. Eight patients (73 per cent) felt completely empty after defaecation. Eight patients (73 per cent) needed to use constipating drugs to control their stool frequency and four patients (36 per cent) needed to adjust their diet. Nine patients (82 per cent) led a completely normal life in terms of return to work and social activities.

Comparison with conventional manual anastomoses (*Table 2*). The retrospective comparison with patients who had undergone conventional transanal hand-sewn anastomoses shows no difference in most respects, apart from a significant decrease in night evacuation in the stapled group ($P<0.01$).

Discussion

The last decade has seen a revolution in the surgical treatment of ulcerative colitis. By use of mucosal proctectomy and pelvic pouch formation, a permanent ileostomy is avoided, the disease is eradicated and gastrointestinal continuity and continence is restored. The challenge that remains is to restore function to as near normal as possible.

Several important lessons have been learnt. An early problem with Parks' original S pouch was that 50 per cent of patients failed to empty the pouch spontaneously[11]. This was due to the length of the efferent spout[12], and its reduction to less than 2 cm has virtually eliminated the problem[2,12,13]. It was also realized that the length of anorectum required to be denuded of mucosa could be reduced from 10–12 to 4–5 cm without impairment of function and with a concomitant reduction in sepsis[14]. Another important lesson has been that patience by both patient and surgeon is required during follow-up, as function improves with time[2]. Similarly, it has been appreciated that function is positively correlated with the compliance and capacity of the pouch, hence the enthusiasm for larger volume pouches[13,15]. Despite these improvements there is still an appreciable number of patients who leak mucus or faeces or both, particularly at night. Also some patients experience an urgency of defaecation which is similar to that experienced before operation. These functional disturbances in part seem to be due to damage to the internal anal sphincter. Most workers who have performed manometry on their patients before and after surgery or have compared them with a control group have found that internal anal sphincter function has been compromised[3–5]. Further, this has not been a temporary defect, as resting anal pressure has remained low even after a 12 month period[3,15]. It has been assumed that this defect is due to direct trauma to the internal anal sphincter during removal of the mucosa and during prolonged anal retraction which is necessary in order to gain access for this manoeuvre. Indeed Keighley and his colleagues have demonstrated that function can be markedly improved if the mucosectomy is performed entirely from above without anal retraction[16].

The stapling technique was devised mainly to reduce internal sphincter damage by the elimination of the mucosectomy and the need for anal retraction. Surprisingly, this thesis has not been proved because there was a significant reduction in resting anal pressure. It is interesting to note that the experience of Johnston *et al.* with a similar stapling technique showed a

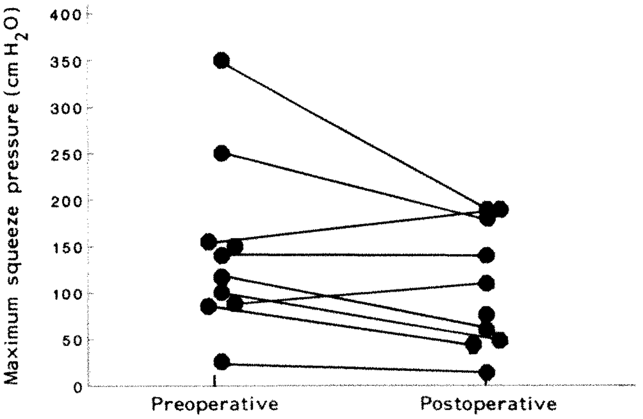

Figure 4 *Maximal squeeze anal canal pressure before and after stapled pouch–anal anastomosis. There is no significant difference between preoperative and postoperative values*

Table 2 *Comparison of clinical function between stapled and manual transanal pouch–anal anastomosis*

	Stapled	Transanal
No. of patients	11	12
Median bowel frequency (per day)	6	6
Range	2–15	4–12
Nocturnal evacuation	*5/11 (45)	12/12 (100)
Continence		
Perfect	7/11 (64)	6/12 (50)
Minor leak	3/11 (27)	5/12 (42)
Major leak	1/11 (9)	1/12 (8)
Spontaneous evacuation	9/11 (82)	9/12 (75)
Using medications	8/11 (73)	9/12 (75)
Unrestricted social life	9/11 (82)	9/12 (75)

Values in parentheses are percentages. * $P<0.01$ (stapled *versus* conventionally hand-sewn anastomoses) reduction in maximal resting anal pressure indicative of internal anal sphincter damage[7]. However, this reduction was less pronounced than that which has occurred in the present study.

It is difficult to explain why in our hands the stapled anastomosis produces such damage to the internal anal sphincter. It must be assumed that the brunt of the injury is due to the dissection and mobilization of the anorectum which may damage the extrinsic autonomic nerve supply which plays such an important part in internal sphincter function[17]. Also the transection of the rectal wall, at the level of the levator ani muscles, may cut through the layer of specialized circular muscle which forms the internal anal sphincter. The damage so inflicted will involve the intramural nerve plexus and blood supply as well as the muscle itself. Whereas a transection at a higher level is unlikely to produce direct damage to the internal sphincter, at this lower level such damage is presumably inevitable. Differences in results between series may therefore be related to the depth of anorectal dissection and the level of transection. It is of interest to note that there was also a fall in the squeeze pressures and, although this was not a statistically significant reduction, it suggests that the technique may in future be found to inflict similar damage on the external anal sphincter. No doubt sphincter damage could be avoided if the mobilization and transection of the rectum was not carried out to a low level, yet this would leave more than the 1–2 cm of anorectal mucosa, and such a policy would increase the risk of cancer development. As it is, this risk must be slightly greater than after the complete mucosal excision achieved during conventional mucosectomy. However such a small area is easily accessible by both digital and sigmoidoscopic examination and should not pose difficulties for assessment. Nevertheless strict surveillance of these patients will be necessary.

Despite the impairment of anal sphincter activity, bowel function after the operation appears satisfactory and marginally superior in the stapled group compared with that achieved after the conventional operation. Certainly night evacuation was significantly reduced. The modified stapling technique was also devised to avoid the use of purse-string sutures, and eliminate the concomitant problems[8]. It ensured that complete 'doughnuts' of tissue were obtained in each patient. It remains to be seen whether the incidence of anastomotic complications will be changed by using the modified technique.

Despite greater confidence in achieving a satisfactory pouch–anal anastomosis, a covering ileostomy seems to be advisable, not to prevent anastomotic dehiscence but to limit its effect should it develop.

It is too early to say from current studies that a stapled pouch–anal anastomosis is superior to the conventional trans-anal mucosectomy and manual pouch–anal anastomosis. A prospective controlled trial will be needed. There is no doubt that the technique we describe is quicker and easier to perform than the conventional procedure, and this is likely to encourage its more widespread use; however, internal anal sphincter function is impaired and anorectal mucosa is left. Both these defects may in the future limit its use.

Acknowledgements

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Predicting local recurrence of carcinoma of the rectum after preoperative radiotherapy and surgery

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A prospective study of prognostic factors has been carried out in a group of 186 patients with tethered rectal carcinomas. Of these, 97 were randomized to surgery alone and 89 to receive preoperative radiotherapy (20 Gy in four fractions). DNA ploidy was determined by flow cytometry. DNA aneuploidy was detected in 60 patients (62 per cent) in the surgery only group, but in only 33 patients (37 per cent) after radiotherapy ($P<0\cdot01$). *There was a significant reduction in local recurrence in irradiated patients* ($P<0\cdot0001$). *DNA diploid tumours were less likely to recur locally. This was more marked in the radiotherapy group* ($P=0\cdot01$) *than in the surgery only group* ($P=0\cdot06$). *After radiotherapy, only the surgeons' assessments of a 'curative' resection and DNA ploidy were independent predictors of local recurrence in multivariate regression analysis, whilst Dukes' classification was not. In conclusion, DNA ploidy may indicate response to radiotherapy and is an important predictor of subsequent local tumour progression.*

Keywords: Rectal cancer, radiotherapy, DNA ploidy, flow cytometry

There has been little change in the prognosis for patients with rectal cancer since the middle of this century. It may be possible to improve the results of surgery[1] but it is unlikely that advances in surgery alone will have a major impact on survival. Consequently, there is a need for effective adjuvant therapy for patients for whom surgery is not curative. Radiotherapy can cure small tumours in the lower rectum[2] and provides useful palliation for patients with symptomatic advanced disease[3]. There may also be a role for radiotherapy as an adjuvant to surgery administered either before or after operation[4–6]. As alternative forms of treatment are developed there is a need to identify factors which help to select those patients likely to benefit and which predict subsequent tumour progression. This study investigates tumour DNA ploidy, determined by flow cytometry[7], in patients with rectal carcinomas in a randomized trial of preoperative radiotherapy, and assesses its value as a predictor of response.

Patients and methods

Patients

The North West Rectal Cancer Trial is a prospective multicentre study designed to evaluate adjuvant preoperative radiotherapy in patients with locally advanced, tethered rectal carcinomas. Patients were recruited between 1982 and 1986; 141 were randomized to surgery only and 143 to adjuvant radiotherapy (20 Gy in four daily fractions using a 4 MeV linear accelerator) immediately before resection. Surgery was performed at the referral hospital and radiotherapy was administered at the regional radiotherapy centre (Christie Hospital). The operating surgeon reported a 'curative' resection if the carcinoma was resected and there was no macroscopic evidence of residual local disease or distant metastases. Dukes' classification was determined at the referring hospital but histological grade was reassessed by a single pathologist to exclude interobserver variation. Patients have been subject to regular review and carcinoembryonic antigen measurements. Local recurrence was diagnosed by clinical examination and computed tomography. Patients with elevated carcinoembryonic antigen levels also had a computed tomographic (CT) scan. Pathological material for flow cytometry was obtained for 97 patients in the surgery only group and 89 in the radiotherapy group, representing patients from the main referral centres. A total of 98 patients from other centres were excluded because of difficulty in obtaining archival pathological material for reassessment. Patients were randomized within hospitals, so those studied by flow cytometry are representative of the whole group.

Flow cytometry

Samples for flow cytometry were prepared using routinely processed histological specimens, fixed in formol–saline and paraffin-embedded[7,8]. Sections 50 μm thick were dewaxed in xylene, rehydrated through decreasing concentrations of ethanol and washed in distilled water. Nuclei were released by cytoplasmic digestion using 0·5 per cent pepsin in 0·9 per cent NaCl, pH 1·5. Samples were centrifuged and the nuclear pellets resuspended in 1 μg of 4′,6-diamidino-2-phenylindoldihydrochloride (DAPI) per ml of RPMI (Rosewell Park Memorial Institute) tissue culture medium. Suspensions were filtered through 35 μm nylon mesh and analysed on a Coulter EPICS V (Coulter Electronics Luton, UK) flow cytometer using ultraviolet (357 nm) excitation. From each sample 20 000 nuclei were analysed and DNA histograms were constructed. The full peak coefficient of variance of the diploid peak was calculated using the incorporated software. DNA aneuploidy was defined as the presence of at least two distinct G0/G1 peaks[9], provided the abnormal peak contained at least 10 per cent of the total number of nuclei analysed. The DNA index was determined by dividing the mode channel of the aneuploid peak by that of the diploid peak. The proportion of aneuploid nuclei was calculated as a percentage of the total number of nuclei analysed.

Statistics

Statistical comparison was made using the χ^2 test and Mann–Whitney *U* test. Survival information up to 30 months is available for 172 patients having DNA ploidy measurements. Survival curves were constructed using the life table method. For local recurrence free survival curves, patients dying without local recurrence were treated as censored observations at the time of death and cumulative proportions local recurrence free, calculated for those at risk. Univariate survival analysis was performed using the log rank test and the independent prognostic significance of variables was determined by Cox's multivariate regression analysis.

This study was supported by the North West Regional Health Authority and the Cancer Research Campaign. Members of the North West Cancer Group are listed in the Appendix to this paper.

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Results

DNA ploidy

A mean of 2·4 blocks was analysed from each tumour. The mean(s.d.) coefficient of variance was 7·3(1·8) per cent. DNA aneuploidy was detected in 60 of 97 (62 per cent) tumours in the surgery only group but in only 33 of 89 (37 per cent) tumours after radiotherapy ($\chi^2=10{\cdot}42$, $P<0{\cdot}01$). The distribution of DNA aneuploid tumours according to the DNA index was similar in both groups, being clustered around the triploid and hypotetraploid levels. The proportion of nuclei in DNA aneuploid peaks was significantly higher in the surgery only group (mean 30·0 per cent, s.d. 13·5) compared with the radiotherapy group (mean 24·2 per cent, s.d. 10·9; Mann–Whitney *U* test, $P=0{\cdot}03$).

Survival

The survival rates for patients in the surgery only and radiotherapy groups were similar and most deaths were due to the progression of distant metastases outside the radiotherapy fields. However, there was a highly significant reduction in the number of local recurrences in the radiotherapy group (*Figure 1*). There was a survival advantage for patients with DNA diploid tumours in the surgery only group; 67 per cent of patients with DNA diploid tumours were surviving compared with 43 per cent of patients with DNA aneuploid tumours ($P=0{\cdot}04$). In the radiotherapy group there was a non-significant DNA diploid survival advantage ($P=0{\cdot}18$) The prognostic significance of other clinical and pathological variables in univariate analysis is shown in *Table 1*. Variables of independent prognostic significance by regression analysis in the surgery only group were: Dukes' classification ($P=0{\cdot}0006$), the surgeons' assessments of a 'curative' resection ($P=0{\cdot}003$) and histological grade ($P=0{\cdot}02$). In the radiotherapy group the only independent prognostic factors were 'curative' resection ($P=0{\cdot}0005$) and Dukes' classification ($P=0{\cdot}002$). DNA ploidy did not confer independent prognostic information for survival in either group.

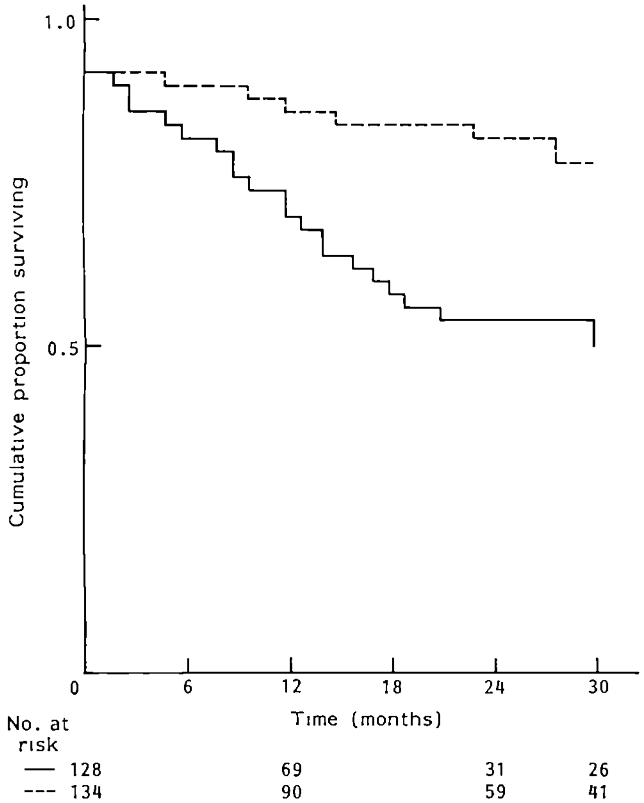

Figure 1 *Cumulative proportional survival. Local recurrence free surgery only compared with radiotherapy patients, —— surgery only, --- radiotherapy,* $\chi^2=17{\cdot}33$, *1 d.f.*, $P<0{\cdot}0001$

Table 1 *The prognostic significance of clinical and pathological variables*

Variable	Control (*P* value)	Radiotherapy (*P* value)
Resection ('curative' *versus* 'non-curative')	<0·0001	<0·0001
Dukes' classification	<0·0001	0·0001
Histological grade	0·005	n.s.
DNA ploidy	0·04	n.s.

P values obtained using univariate life table analysis at 30-month follow-up; n.s., not significant

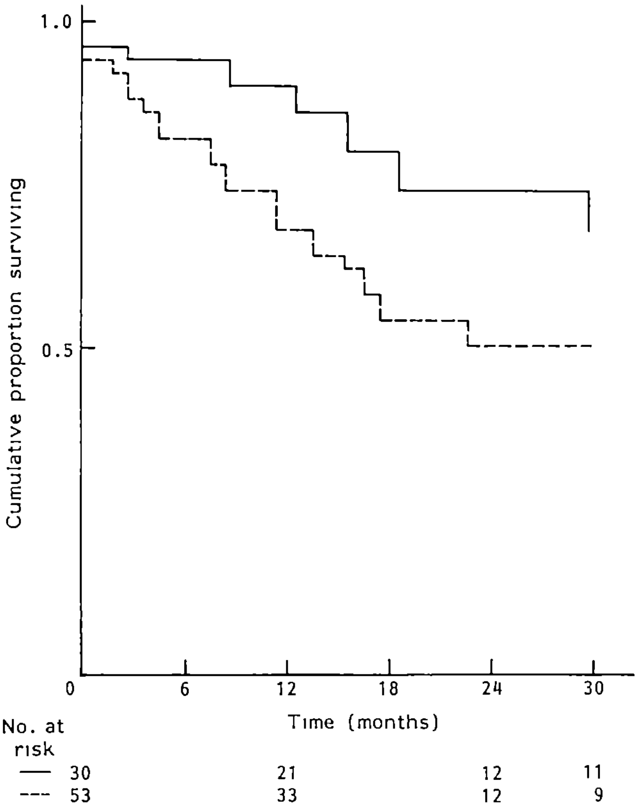

Figure 2 *Cumulative proportional survival in surgery only patients Local recurrence free. DNA diploid compared with DNA aneuploid, —— diploid, --- aneuploid,* $\chi^2=3{\cdot}67$, *1 d.f.*, $P=0{\cdot}06$

Local recurrence

There was a DNA diploid local recurrence free advantage for patients with DNA diploid tumours in the surgery only group Of those at risk, the cumulative proportions local recurrence free were 68 per cent of patients with DNA diploid tumours and 50 per cent with DNA aneuploid tumours ($P=0{\cdot}06$; *Figure 2*). DNA ploidy status after radiotherapy was a more powerful predictor of local recurrence, 90 per cent of at risk patients with DNA diploid tumours were free of local recurrence compared with 58 per cent of patients with DNA aneuploid tumours ($P=0{\cdot}01$; *Figure 3*). The relationship between other clinical and pathological features and local recurrence in univariate analysis is shown in *Table 2*. Independent predictors for local recurrence in the surgery only group were: Dukes' classification ($P=0{\cdot}00003$), DNA ploidy ($P=0{\cdot}002$), 'curative' resection ($P=0{\cdot}01$) and age ($P=0{\cdot}03$). After radiotherapy the only independent predictors of local recurrence were 'curative' resection ($P=0{\cdot}000008$) and DNA ploidy ($P=0{\cdot}003$).

DNA aneuploid subgroups

DNA aneuploid subgroups were defined according to DNA index; either 1·1–1·8 or 1·9–2·1 (DNA 'tetraploid') and

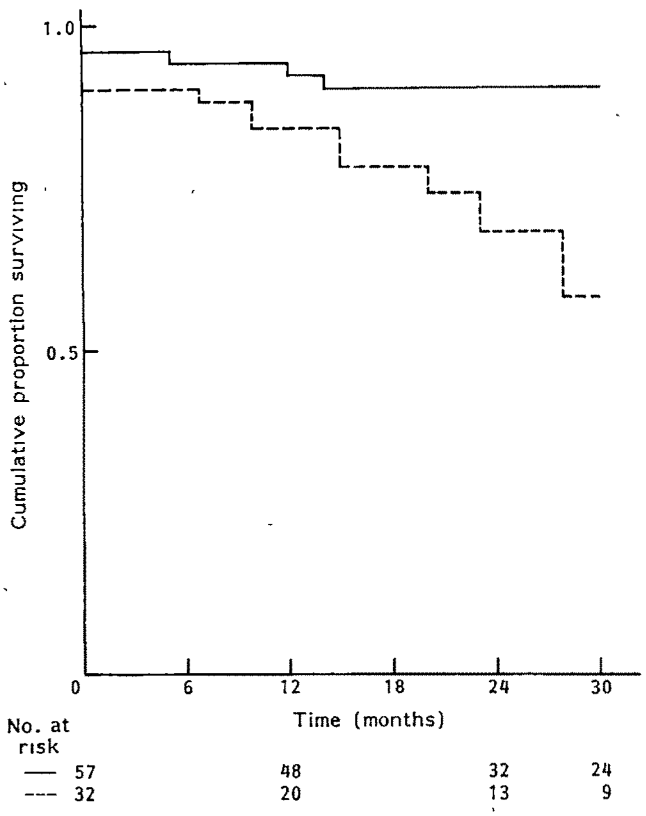

Figure 3 *Cumulative proportional survival in radiotherapy patients. Local recurrence free: DNA diploid compared with DNA aneuploid;* —— *diploid;* --- *aneuploid;* $\chi^2=6{\cdot}09$, *1 d.f.*, P = 0·01

Table 2 *The predictive significance of clinical and pathological variables for local recurrence at 30-month follow-up*

Variable	Control (*P* value)	Radiotherapy (*P* value)
Resection ('curative' *versus* 'non-curative')	0·0003	0·0002
Dukes' classification	<0·0001	0·005
Histological grade	0·03	n.s.
DNA ploidy	0·06	0·01

P values obtained using univariate analysis; n.s., not significant

aneuploid peak size[10], but these did not confer any additional prognostic information.

Discussion

The measurement of cellular DNA content by flow cytometry is emerging as a potential aid in the pathological assessment of human tumours. In colorectal cancer most investigators report a survival advantage for patients with DNA diploid tumours[7], but, to date, this prognostic information has found little clinical application. In the present study, the incidence of DNA aneuploidy and the DNA diploid survival advantage for patients treated by surgery alone are in keeping with earlier studies of primary colorectal carcinomas[7]. After radiotherapy the detection of DNA aneuploidy decreased, reflecting local response to treatment with the eradication of DNA aneuploid cells in a proportion of tumours. Radiotherapy reduced local recurrence, although survival was unaffected as most deaths were due to the progression of distant metastases outside the radiation field. The local recurrence rates were high, reflecting the locally advanced nature of tumours at entry into the trial. They are comparable to those in patients with advanced carcinomas in other studies[11,12] and emphasize the need for effective surgery[1] and adjuvant therapy. The postirradiation DNA ploidy status ceased to be a significant predictor of survival because changes in DNA ploidy status were not matched by altered survival rates. Therefore, if DNA ploidy is used to predict survival the information should be obtained before radiotherapy.

The DNA ploidy status of a tumour after radiotherapy was an important predictor of local tumour progression. If DNA aneuploidy is detected after radiotherapy, viable tumour cells are still present and repopulation of residual tumour and local recurrence will occur. After radiotherapy the predictive power of DNA ploidy for local recurrence increased in contrast to conventional histology which decreased. Radiotherapy induces tumour necrosis which may cause difficulties in the histological assessment of the primary tumour and lymph nodes within the radiotherapy fields. This probably accounts for the downstaging of rectal cancers observed after radiotherapy[5].

The response to radiotherapy was not uniform suggesting that there are biological differences in radiosensitivity. The greatest response appeared to be in those DNA aneuploid tumours where the aneuploid population was eradicated. Dyson *et al.*[13] studied DNA ploidy in patients with carcinoma of the uterine cervix treated by radiotherapy and suggested that DNA aneuploid tumours were more radiosensitive than DNA diploid tumours. The reasons for differences in sensitivity are uncertain but may reflect different proliferative rates and stability. There are insufficient data at present to select rectal cancer patients for radiotherapy on the basis of DNA ploidy but those with DNA aneuploid tumours appear most likely to benefit.

In conclusion, DNA ploidy measurements are readily obtained using routinely processed pathological specimens and could be used to stratify patients in radiotherapy trials. DNA ploidy may indicate response to preoperative radiotherapy and is an important predictor of subsequent local tumour progression.

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Appendix

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Endoluminal ultrasound for early detection of local recurrence of rectal cancer

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The diagnostic potential of endoluminal (endorectal and endovaginal) ultrasound to detect asymptomatic resectable local recurrence after rectal cancer surgery has been assessed in 120 patients: 17 recurrences (14 per cent) were detected. The method showed 97 per cent accuracy, 94 per cent sensitivity and 98 per cent specificity; the positive predictive value was 85 per cent and the negative predictive value was 99 per cent. A longer follow-up is, however, necessary to confirm these results. Of the 17 patients with local recurrence, six were asymptomatic and underwent reoperative surgery. Of the other 11 patients with symptomatic recurrence, only two underwent reoperative surgery.

Keywords: Rectal cancer, local recurrence, endoluminal ultrasound

Despite a better understanding of the natural history of large bowel cancer and the availability of stapling devices[1,2], the 5-year survival rate of patients operated on for rectal cancer remains approximately 50–60 per cent[3,4]. This is due in large measure to the frequent development of distant metastases[5] and local recurrence[6,7]. While distant metastases represent the expression of systemic disease, local recurrence may be due to a failure of surgery and is an outcome that is dismaying for any surgeon who believed that a radical clearance of tumour had been achieved.

Local recurrence usually occurs early (70–80 per cent of recurrences become manifest within 2 years of surgery[2,4,8]) and with a variable but high incidence (6–32 per cent)[1,3,4,6,9–12]. The incidence rises even higher (to 38 per cent) with longer postoperative follow-up and when autopsy studies are performed to detect clinically undetectable recurrence[13]. Local recurrence is particularly troublesome to the patient as it frequently causes an earlier and more painful death than metastases[14]. The most important factor associated with such recurrence now seems to be the local and, in particular, the lateral spread of the primary tumour[15,16].

Prevention is undoubtedly the best 'treatment' for local recurrence[17–19]. The poor results of reoperative surgery for symptomatic recurrence have led many to believe that the primary operation is the best opportunity available to the surgeon[14]. However, one must also be prepared to deal with recurrence when it develops, especially as local recurrence, even when it is the only site of redevelopment of the disease[14], is often the cause of death. Reoperative surgery offers the only method of obtaining good palliation and in some cases may even result in cure[14]. Such curative reoperative surgery depends mainly on the early detection of recurrence[4,14,20].

We have evaluated the diagnostic potential of endoluminal (endorectal and endovaginal) ultrasound in the postoperative follow-up of patients who have had surgery for rectal cancer, in an attempt to detect recurrence at an early stage, thus allowing potentially curative surgery

Patients and methods

We performed endoluminal ultrasonography in 120 patients (69 male, 51 female) operated on for rectal adenocarcinoma at from 3 to 14 cm from the anocutaneous line. Seven patients underwent local excision, 90 had an anterior resection and 23 had abdominoperineal excision of rectum. All patients were studied by a single observer (D M.) and the examination was performed on an outpatient basis with each examination lasting an average of 15 min.

The 1850 Bruel and Kjaer radial probe (Bruel and Kjaer, Naerum, Denmark) was used. Its diameter was 1 8 cm (in cases of stenosis a 0 5 cm diameter probe was preferred). The total length of the probe was about 24 cm. A 7 MHz transducer (focal length 2–5 cm) was generally employed, but if recurrence extended further a 4 MHz transducer with a longer focal length (3–7 cm) was used. If stenosis was present, the examination was performed with an antegrade view transducer of 5·5 MHz. The transducer was encased in a thin rubber balloon and filled with 50–60 ml degassed water, which distended the rectal wall and produced acoustic contact with it. The transducer rotated at a rate of 4–6 cycles per second with a 360° display of the rectal wall and surrounding tissues.

After following a low roughage diet for 2 days, the patient was given an enema to empty the rectum and was then examined, with full bladder, in a left lateral decubitus position. The probe was covered with acoustic coupling gel and inserted, after digital exploration, into the rectum through a rigid rectoscope 20 mm in diameter, which allowed a safe, high insertion. In this way the probe could be positioned as far as 20 cm beyond the anocutaneous line, the limit depending on the anatomical modifications caused by the operation. A scale on the probe indicated the distance from the anocutaneous line. The examination started from the point furthest from the anus. The rectal wall and, in particular, the perirectal spaces (ischiorectal and pelvirectal fossae and presacral space) were examined by slowly withdrawing the probe towards the anal canal. Comparison between ultrasound images obtained in preoperative staging of rectal tumours and those from operative specimens has demonstrated that neoplastic tissue usually appears as a hypoechoic, non-homogeneous mass with well defined margins[21,22] (*Figures 1* and *2*). The patient was first examined about 30 days after surgery to delineate the new anatomical conformation, and the images thus obtained were compared with those at subsequent examinations.

In our follow-up regimen, patients at high risk of recurrence (Astler and Coller's stages B2, C1 and C2)[23] were usually assessed for the first 2 years with the following techniques. Liver ultrasonography and estimation of the tumour markers carcinoembryonic antigen, gastrointestinal cancer antigen and tissue polypeptrol antigen were carried out every 3 months. Pancolonoscopy and chest radiography were performed every 6 months, and pelvic and abdominal computed tomography and bone scintigraphy were performed yearly These high risk patients were also evaluated by endoluminal-ultrasonography at 3-monthly intervals for the first 2 years and then at 6-monthly intervals for another 3 years. In the case of a radical local excision, ultrasound examination was performed every 2 months and a biopsy was taken every 4 months.

In female patients with anteriorly located recurrences, the endorectal examination was complemented with endovaginal ultrasonography (*Figures 3* and *4*). In female patients who had undergone an abdominoperineal excision of rectum, we performed the ultrasound examination *per vaginam* every 3 months, and combined it with pelvic computed tomography every 6 months. When an image raised a suspicion of recurrence, the examination was repeated after 40–50 days; if the mass was still present or increased in size, biopsy was performed. For a completely extramural mass, echo-guided biopsy was performed with a Tru-Cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) needle inserted transrectally, transvaginally or, more frequently, by a transperineal route. For echo-guided biopsy we often

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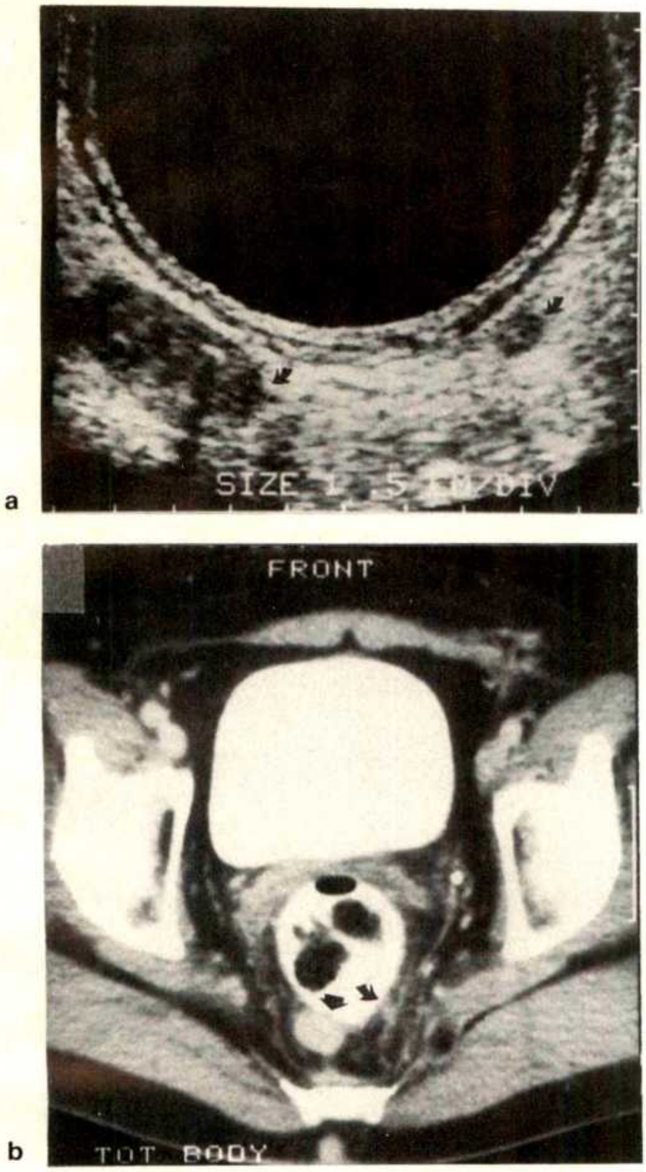

Figure 1 **a** *Endorectal ultrasonography demonstrates the presence of two hypoechoic non-homogeneous extramural posterior masses (arrowed: diameters of 19 and 5 mm).* **b** *Pelvic computed tomography confirms the presence of the two masses*

used the sectorial 7 MHz probe which allowed better visualization of the needle. If the mass was intramural but not yet protruding into the rectal lumen, biopsy was performed endoscopically, even on an apparently healthy mucosa, at the site indicated by ultrasound (*Figure 5*).

Patients with recurrence were classified into three groups[24] as follows: group 1 included asymptomatic patients in whom recurrence was not demonstrated by any means other than by endoluminal ultrasonography; group 2 included symptomatic patients in whom local recurrence was confirmed by endoluminal ultrasonography but not by digital exploration and/or colonoscopy and/or pelvic computed tomography; group 3 comprised symptomatic patients in whom one or more of the above diagnostic methods, other than endoluminal ultrasonography, detected recurrences which were then confirmed by endoscopic or computed tomographically guided biopsy.

Results

Of 120 rectal cancer patients undergoing endoluminal ultrasound examination during the period from January 1986 to January 1988, recurrence was detected in 17 cases (14 per cent). All of these patients were examined on a minimum of two occasions after operation. No significant complications were related to the ultrasound examination.

The procedure showed 97 per cent accuracy, 94 per cent sensitivity and 98 per cent specificity. The negative predictive value was 99 per cent and the positive predictive value was 85 per cent. Although endoluminal ultrasonography was routinely repeated after 40–50 days in order to confirm an initial suspicion of recurrence, the positive predictive value of 85 per cent was still unsatisfactory, and biopsy for confirmation was always performed. We have had two apparent false positive ultrasound results, one of which was disproved by echo-guided biopsy and the other by second-look surgery. These patients, however, are still being followed closely and may yet prove to have local recurrence. We had one false negative result in a patient whose recurrence was confirmed by endoscopic biopsy; this patient had a stenosis which permitted the use of only the antegrade view 5·5 MHz transducer. Echo-guided biopsy was performed in nine patients (one transrectally, two transvaginally and six transperineally) and confirmed the presence of recurrence in eight. However, in three of these patients it was necessary to perform a second biopsy to obtain a positive result. Biopsy in the remaining patient proved to be negative.

Out of 17 recurrences detected by endoluminal ultrasonography, 12 were diagnosed by endorectal and five by endovaginal ultrasonography (*Table 1*). The six asymptomatic patients in group 1 had further surgery. Five of these recurrences which were detected by endorectal ultrasound were treated by abdominoperineal excision of rectum (four were 'curative' and one was palliative). The remaining patient, a woman already

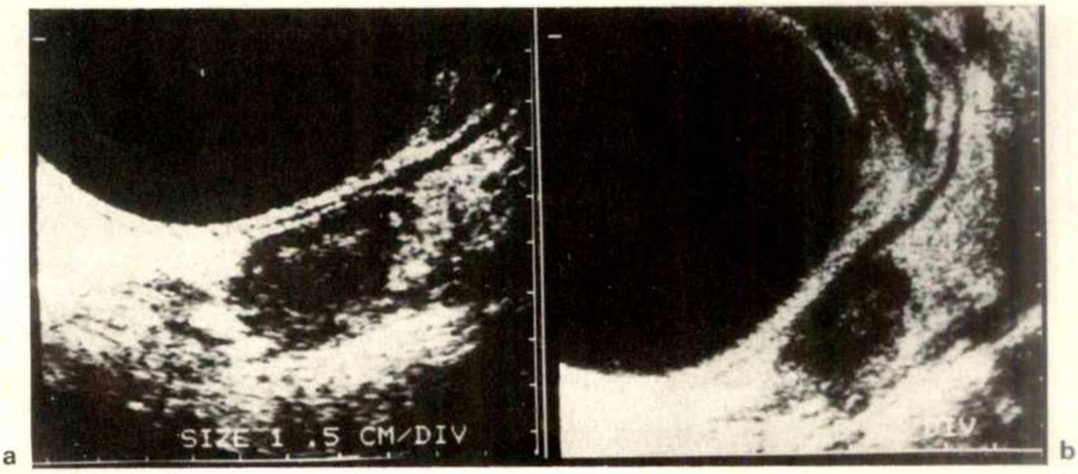

Figure 2 **a** *Endorectal ultrasonography reveals the presence of a perianastomotic extramural hypoechoic and non-homogeneous mass (diameter 1·5 cm) in the left posterolateral site.* **b** *The same case: endorectal scan at a higher level shows the infiltration of the muscularis propria by the extrarectal mass*

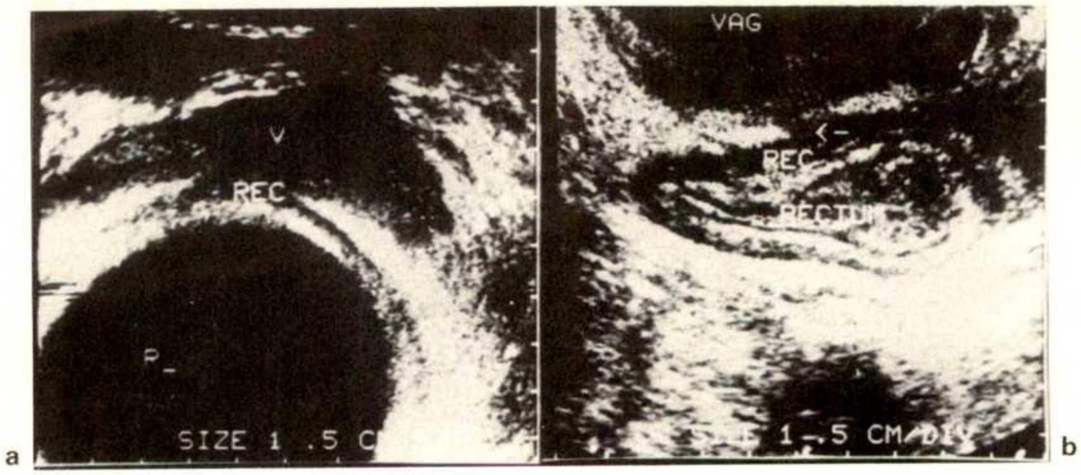

Figure 3 **a** *Recurrence infiltrating the posterior wall of the vagina from the anterior rectal wall. V, vagina; REC, recurrence; R, rectum.* **b** *The examination* per vaginam *confirms this infiltration more accurately. VAG, vagina; REC, recurrence*

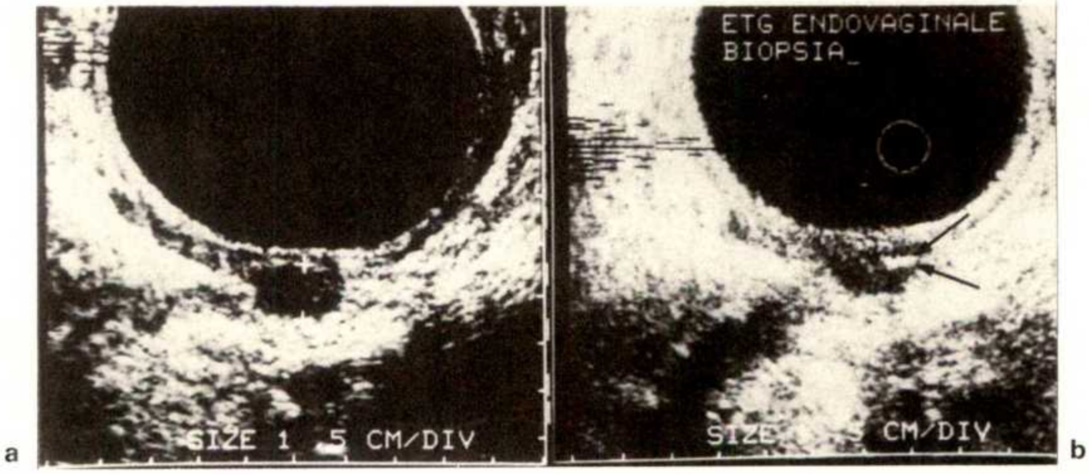

Figure 4 **a** *Endovaginal ultrasonography demonstrates the presence of a small mass (diameter < 1 cm) immediately external to the posterior wall of the vagina.* **b** *Echo-guided transperineal biopsy confirms the diagnosis of recurrence (arrows indicate the biopsy needle)*

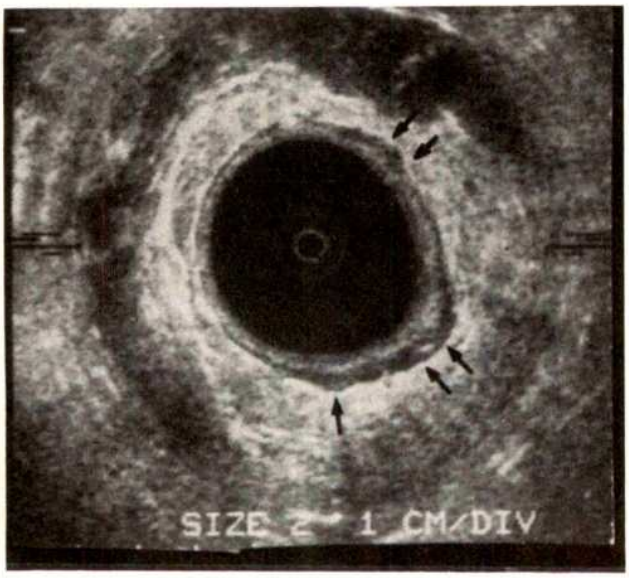

Figure 5 *Endorectal ultrasound: the rectal wall appears hypoechoic, thickened and irregular externally. Biopsy of the apparently healthy mucosa confirmed the diagnosis of recurrence (arrows)*

treated with a Miles' operation, underwent 'curative' resection of a small recurrence detected by endovaginal ultrasound.

The operative specimens confirmed the presence, localization and size of the recurrences detected by endoluminal examination. In all six asymptomatic patients, recurrences were localized only in the pelvis (one intraparietal, two in the rectosacral space, one in the pelvirectal fossa, one between the rectum and the vagina, and one posterior to the vagina). All of these recurrences, which were treated by further surgery, were found to be less than 3 cm in diameter (range 8–28 mm).

All six patients in group 1 are still alive with a follow-up duration of between 4 and 15 months. In two patients, one of whom underwent 'curative' surgery, relapse was confirmed by computed tomography after 4 and 7 months; the other four patients are apparently still free of disease.

In group 2 there were four recurrences, two revealed by endorectal and two by endovaginal ultrasonography. Only one patient, already treated by anterior resection, underwent palliative abdominoperineal excision of rectum. This patient is still living, albeit with residual tumour, after 4 months. Of the remaining three group 2 patients, two underwent palliative radiotherapy and are both alive, with recurrence, at 12 and 14 months, and one received only supportive treatment and died 3 months later.

Of the seven patients in group 3, digital examination was positive in three cases, endoscopy in four and computed tomography in five. The only patient who underwent surgery was treated by palliative abdominoperineal excision and died after 7 months. Three patients with distant metastases had chemotherapy: two died after 5 and 7 months, and one is alive with recurrence at 13 months. The remaining three patients received only supportive treatment. Two died at 4 and 6 months after the diagnosis of recurrence and one is still alive, with recurrence, 1 year later.

Table 1 *Details of 17 patients with recurrence out of 120 patients studied by endoluminal ultrasonography after surgery for rectal cancer*

Endoluminal ultrasonography*	No. of patients	Treatment	Results	Follow-up (months)	Other positive procedures
Endorectal					
Group 1	5	Curative surgery	Alive, disease-free	15	–
		Curative surgery	Alive, disease-free	12	–
		Curative surgery	Alive, disease-free	11	–
		Curative surgery	Alive with recurrence	7	–
		Palliative surgery	Alive with recurrence	4	–
Group 2	2	Palliative surgery	Alive with recurrence	4	–
		Radiotherapy	Alive with recurrence	12	–
Group 3	5	Palliative surgery	Deceased	7	Colonoscopy
		Chemotherapy	Deceased	5	Computed tomography
		Chemotherapy	Deceased	7	Digital examination Colonoscopy, computed tomography
		Supportive	Deceased	6	Digital examination Colonoscopy, computed tomography
		Supportive	Alive with recurrence	12	Colonoscopy
Endovaginal					
Group 1	1	Curative surgery	Alive, disease-free	8	–
Group 2	2	Radiotherapy	Alive with recurrence	14	–
		Supportive	Deceased	3	–
Group 3	2	Chemotherapy	Alive with recurrence	13	Computed tomography
		Supportive	Deceased	4	Digital examination, computed tomography

* 97 endorectal, 23 endovaginal

Discussion

These findings confirm that the feasibility of reoperative surgery for local recurrence depends not only on the type of operation performed on the primary tumour (abdominoperineal excision does not easily lend itself to reoperation[14,25]) but also on the early detection of recurrence[20]. The possibility of reoperative surgery markedly increases when recurrence is diagnosed in asymptomatic patients, which highlights the importance of careful follow-up[9,26–28]. The proportion of potentially curative reoperative surgery for local recurrence increases from 2–14 to 40 per cent when patients are followed up closely with regular endoscopic assessment[4,8,9,20,27]. The worth of follow-up should not be based on the number of examinations performed each year, but on the actual effectiveness of the methods employed.

It is important to emphasize the difficulty of detecting local recurrence, not only after abdominoperineal excision but also after sphincter-saving resection. In the latter cases endoscopy plays a major part[29], but the frequently extramural growth of recurrences ('iceberg recurrences') does not always permit an early endoscopic diagnosis[4,30]. For this reason, computed tomography is as important after anterior resection as it is after abdominoperineal excision[31,32]. For the early detection of recurrence, frequent assessments are required[32], but the repeated use of computed tomography is undesirable because of radiation exposure and cost.

Endoluminal ultrasonography links much of the diagnostic potential of colonoscopy (endoluminal) and computed tomography (extramural). It is also a particularly favoured technique as it is simple to execute, it can be performed on an outpatient basis, it is well tolerated, it does not involve X-ray exposure, and it is cheap. In summary, endoluminal ultrasonography is ideal for repeated use in the monitoring of the operated patient.

All patients operated on for colorectal cancer can be examined if the probe can reach the level of the anastomosis. In the present study, however, only rectal cancer patients were included. While the routine use of staplers allows more frequent conservative surgery[2], this may require a greater employment of endorectal ultrasound for follow-up. A stapled anastomosis does not adversely affect the ultrasound image in that the visualization of its double hyperechoic row gives a reference point for identification of the anastomosis. In some patients, during surgery on the primary tumour, we positioned the omentum between the rectum and the sacrum to create a 'thickness' with the intent of facilitating the postoperative ultrasonic study of the rectosacral space (the area with the highest risk for development of recurrence). The usefulness of this surgical procedure has still to be confirmed.

When recurrence protrudes into the rectal lumen, colonoscopy is a more useful technique than ultrasonography. However, in the early stages, recurrence is often represented by a thickening of the rectal wall or, more frequently, by an extraparietal mass. The ultrasound image of such lesions usually consists of a perirectal, round, hypoechoic and non-homogeneous mass, which is completely extramural in the early stages with later infiltration of the rectal wall. Differentiation between postoperative fibrosis and recurrence is not always easy; subsequent morphological and volumetric changes are of the utmost importance.

Whenever a recurrence is suspected, it should always be proved with biopsy, but this is performed only after two or more abnormal examinations to avoid excessive invasive testing. Of the 120 rectal cancer patients undergoing postoperative endoluminal ultrasonography, we observed only two false positives and one false negative. These results should be critically evaluated in view of the fact that ultrasonic diagnosis cannot be easily contradicted by other diagnostic procedures or by second-look surgery. A longer follow-up may temper present optimism.

Although endoluminal ultrasonography may allow early diagnosis and potentially curative revisional surgery, it may also have a place when recurrence has already been diagnosed by other methods. The ultrasound examination may confirm and more accurately define the extent of neoplastic infiltration. When radiotherapy is required, ultrasound images facilitate a more precise focusing and permit assessment of the efficacy of the treatment by repeated measurement of the size of the lesion.

In conclusion, even though they must be confirmed by larger studies and longer follow-up, our results show that endoluminal ultrasonography should be routinely performed in the postoperative follow-up of rectal cancer patients. The main objective is the early detection of recurrence suitable for 'curative' surgery.

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Lateral internal sphincterotomy in the treatment of fourth degree haemorrhoids

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Between January 1984 and May 1988, 25 patients with fourth degree haemorrhoids were treated in the acute phase by lateral internal sphincterotomy under narcosis. Pain relief was immediate. The median hospital stay was 3 days. The median follow-up period was 26 months. For 20 patients a single lateral internal sphincterotomy alone was adequate treatment. If further therapy was required, simple band ligation was enough. There was one recurrence, which was treated with a further lateral internal sphincterotomy. In the long term, 18 patients had no complaints and seven had only minor complaints. Twenty-three patients were very satisfied and two were moderately satisfied. Nobody was dissatisfied. Lateral internal sphincterotomy is an attractive alternative in the treatment of fourth degree haemorrhoids, its major benefits being simplicity, efficiency and low morbidity.

Keywords: Fourth degree haemorrhoids, lateral internal sphincterotomy

In fourth degree haemorrhoids, according to the classification of Thomson and Leicester[1] (also called 'acute haemorrhoidal disease' or 'attack of the piles'), prolapsed haemorrhoids become trapped in a vicious circle of pain, increased sphincter tone and venous engorgement. Usually the event is incited by straining at stool. It leads to oedema, thrombosis and eventually necrosis of the pile mass (*Figure 1*). The predominant clinical symptom, which is often very dramatic, is pain, and this causes the patient to consult the physician for relief.

Left unattended, the natural course of events in the majority of cases is one of spontaneous resolution over a period of weeks, leading either to symptomatic improvement of the pre-existing haemorrhoids or, rarely, to large fibroid masses at the anal orifice. Rare complications are necrosis, infection and even portal pyaemia[2].

The usual choice of treatment is between conservative management and emergency haemorrhoidectomy, the latter being the standard against which alternatives must be compared[3–9].

This study investigated the role of lateral internal sphincterotomy as an alternative treatment, which avoids the early morbidity and late sequelae of classical haemorrhoidectomy.

Patients and methods

Between January 1984 and May 1988 25 patients with fourth degree haemorrhoids were seen at the St. Elisabeth Hospital. These comprised 16 men and nine women of median age 44 years (range 13–81 years). All were treated by lateral internal sphincterotomy.

Lateral internal sphincterotomy was performed under general anaesthesia, with the patient in the jack-knife position. After preliminary infiltration with a diluted adrenaline solution, the internal sphincter was exposed laterally (*Figure 2*) and divided with scissors up to the level of the dentate line (open lateral subcutaneous sphincterotomy[1]). For reasons of haemostasis, the right lateral approach, between the anterior and posterior piles, was usually appropriate. Subsequently prolapse was, whenever possible, reduced.

Results

Postoperative morbidity

There was a consistent, immediate and dramatic relief of pain. Oedema, thrombosis and prolapse remained for a varying length of time but gradually subsided in the few days after surgery. The median hospital stay was 3 days (range 0–13 days).

Additional therapy

For 20 of the 25 patients a single lateral internal sphincterotomy was adequate treatment. For those five patients who needed further therapy because of residual second or third degree haemorrhoids, simple band ligation was done within a few months of lateral internal sphincterotomy. Haemorrhoidectomy was never necessary.

Recurrence

In one case, fourth degree haemorrhoids reoccurred after 26 months. A second lateral internal sphincterotomy was performed and no other treatment was required.

Long-term results

After a median follow-up period of 26 months (range 1–56 months), 18 patients had no complaints about their condition and seven patients had only minor complaints (*Table 1*). Most had to be asked specifically about incontinence of which none complained spontaneously, presumably because of its intermittent and mild nature. At inspection 19 patients had no haemorrhoids, one had first degree haemorrhoids, and five had second degree haemorrhoids. Twenty-three patients were very satisfied, two were moderately satisfied and none was dissatisfied.

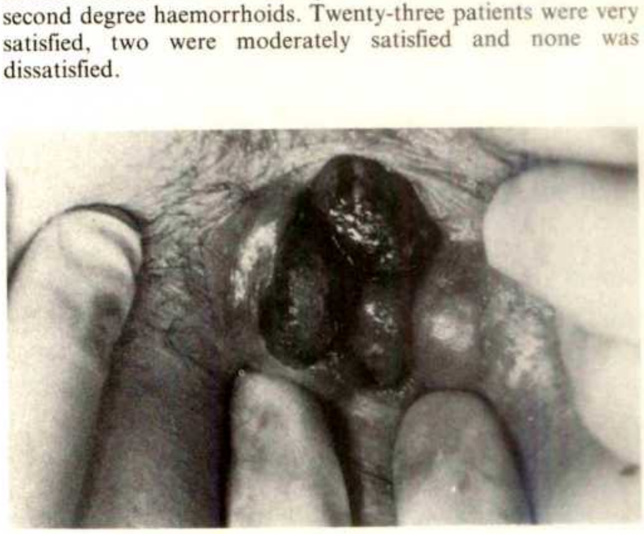

Figure 1 *Fourth degree haemorrhoids*

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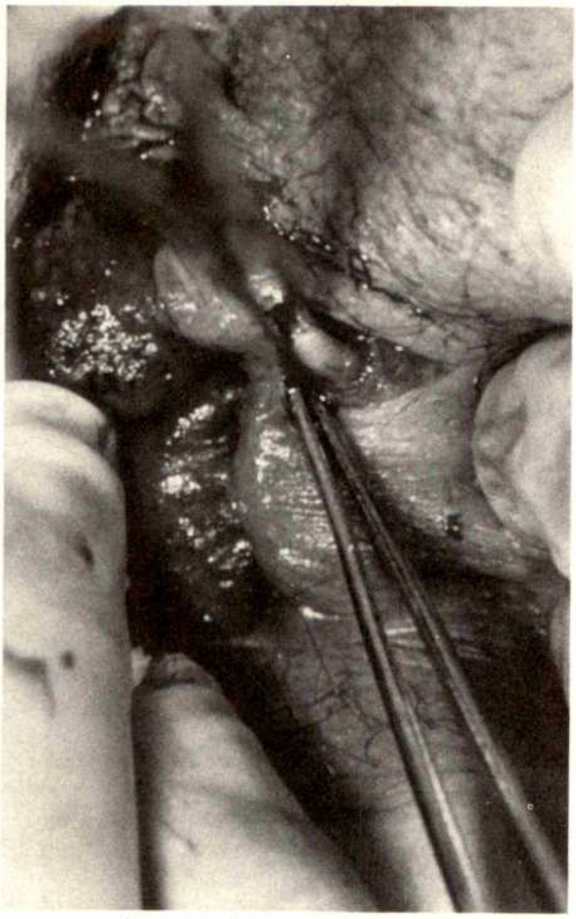

Figure 2 *Lateral exposure of the internal sphincter*

Table 1 *Symptoms complained of by 25 patients at a median follow-up time of 26 months*

Symptom	No. of patients*
None	18
Pain at defaecation	1
Itching	2
'Prolapse'	2
Incontinence of flatus	3

*One patient complained of two symptoms

Discussion

The treatment of haemorrhoids has evolved because of new insight into the anatomy and pathophysiology of the condition. According to Thomson[10] and Haas *et al.*[11], haemorrhoids are vascular cushions supported by connective tissue and secured to the internal sphincter and conjoined longitudinal coat by anchoring connective tissue. This connective tissue deteriorates with ageing and as a result the haemorrhoids not only bulge but also descend into the anal canal. Band ligation and sclerotherapy aim at reducing the vascular cushions to their normal size and resecuring them to the internal sphincter.

The relationship between the internal sphincter and haemorrhoids has attracted the attention of many authors. Allgower[12] stated that venous outflow from the haemorrhoidal plexus partially runs through the internal sphincter and that sphincteric hyperfunction leads to a vicious circle of venous engorgement, pain at defaecation and a further rise in sphincter tone. He reported the results of 111 sphincterotomies for from first to fourth degree haemorrhoids. His success rate was 95 per cent, with six recurrences which were treated by lateral internal sphincterotomy. Hancock[13] and Hancock and Smith[14] noted increased internal sphincter tone in patients with haemorrhoids. Treatment using Lord's procedure gave satisfactory symptomatic improvement and a reduction in resting anal pressure.

Arabi *et al.*[15] found significantly higher anal pressures in patients whose haemorrhoids caused pain and bleeding. These were usually men aged less than 46 years. Read *et al.*[16] noted that the increased internal sphincter tone in patients with haemorrhoids disappeared after haemorrhoidectomy, suggesting it to be the effect rather than the cause of the haemorrhoids. Schouten and van Vroonhoven[17], using lateral internal sphincterotomy in the treatment of patients with from first to third degree haemorrhoids and high anal pressure at manometry, were especially successful in managing patients in whom pain and bleeding were the main presenting symptoms. Gibbons *et al.*[18] found increased maximum resting pressures in patients of both sexes with second or third degree haemorrhoids, although this reached statistical significance only in men.

Lateral internal sphincterotomy is well known to be a simple, effective way of reducing internal sphincter tone without impairing its function[1,17]. Because of this we have adopted this technique along with band ligation in our treatment for from first to third degree haemorrhoids (*Table 2*), and the present study has examined its use in fourth degree haemorrhoids.

Our reasons for not treating fourth degree haemorrhoids classically with emergency radical haemorrhoidectomy are twofold. Firstly, like others, we find haemorrhoidectomy more difficult in the acute condition, and it is certainly not an operation for the inexperienced. There is especially the risk of causing inadequate skin bridges between the haemorrhoidectomy wounds, which predisposes to anal stenosis. To avoid this complication Mazier[9] advocated maximal three-quadrant excisions, Hansen and Jorgensen[6] usually excised not more than two piles, and Heald and Gudgeon[7] advised limited haemorrhoidectomy with excision of only the largest prolapsed haemorrhoid. Obviously it is not necessary to excise all prolapsed tissue to achieve good results: debulking is sufficient. Secondly, emergency radical haemorrhoidectomy is associated with postoperative pain and although this may be less than the preoperative pain, or the pain associated with conservative management, it may still be substantial[8]. In this respect a definite beneficial effect from the addition of an internal sphincterotomy to haemorrhoidectomy has been noted in patients aged under 40 years[8].

In an attempt to avoid these drawbacks of emergency haemorrhoidectomy, we decided to extend our rationale to the treatment of fourth degree haemorrhoids. Lateral internal sphincterotomy performed in the acute condition should interrupt the vicious circle, thereby reducing the fourth degree haemorrhoids to third or second degree haemorrhoids. In due course these could be treated with simple band ligation.

Our results show that treating fourth degree haemorrhoids by lateral internal sphincterotomy leads to immediate relief of pain (confirmed by all patients), a short hospital stay and few long-term complaints. It is usually adequate as a single treatment but if further treatment is eventually required, this may simply consist of band ligation.

In conclusion, we are convinced that lateral internal sphincterotomy is an attractive alternative to emergency haemorrhoidectomy in the management of fourth degree haemorrhoids. Its major benefits are simplicity, efficiency and low morbidity.

Table 2 *Treatment policy with regard to degree of haemorrhoids*

Degree	Patients aged <50 years	Patients aged >50 years
First	Lateral internal sphincterotomy	Band ligation
Second	Lateral internal sphincterotomy	Band ligation
Third	Band ligation	Band ligation

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Prognosis after surgery for colonic Crohn's disease

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The long-term prognosis including operation rates, the incidences of recurrent disease, morbidity and mortality and current status has been analysed in a group of 360 patients with Crohn's colitis grouped according to the primary site of macroscopic disease at diagnosis. The group has been followed from diagnosis for a mean period of 14·9 years. The overall operation rate was 76 per cent. Prolonged spontaneous or drug induced remission occurred at all sites: right-sided disease (11 per cent), extensive colonic disease (21 per cent) and left-sided disease (38 per cent). The cumulative reoperation rates at 5 and 10 years after right hemicolectomy were 26 and 46 per cent, after colectomy and ileorectal anastomosis 46 and 60 per cent, and after panproctocolectomy 10 and 21 per cent, respectively. There was a twofold excess mortality rate from related Crohn's disease deaths during the period of review, but the mortality rate has fallen with time. There have only been 11 related deaths in the last decade, of which eight were probably unavoidable. The current status of most patients is good, although treatment has included a permanent stoma in less than half (41 per cent) the patients still under review. Currently all but 14 patients are well and symptom-free and only 16 are receiving specific medical treatment. Until the aetiology of Crohn's colitis is understood, if medical treatment has failed to resolve symptoms, appropriate surgical treatment in experienced hands is an effective way of restoring patients with chronic persistent symptoms to good health.

Keywords: Crohn's disease, colon surgery, large intestine

There have been few studies of the long-term prognosis of Crohn's disease involving the colon[1–4]. In this study, because there are many variables which influence the interval from diagnosis to initial resection, we have determined the long-term prognosis in all patients but particularly those who have undergone surgical treatment for Crohn's disease involving the colon.

Patients and methods

Among a consecutive series of 779 patients with Crohn's disease under review at the General Hospital, Birmingham, between 1944 and 1986, 360 (46 per cent) at diagnosis had evidence of Crohn's disease involving the large intestine (164 men, 196 women). The mean age at onset of symptoms was 37·2 years (range 3–78 years) with a mean interval from onset to diagnosis of 2·4 years (range 0–20 years). The mean duration of follow-up since diagnosis is 14 9 years.

Diagnosis

The diagnosis of Crohn's disease was confirmed by macroscopic and histological examination of the resected specimens in all 272 patients undergoing resection. Of the 88 patients treated conservatively, 74 had the clinical and radiological features of Crohn's disease (including 30 with granulomas on histological examination of rectal biopsy), 13 patients were diagnosed on histological examination of the rectal biopsy and one was diagnosed on the macroscopic appearance at laparotomy. The first radiological endoscopic or histological evidence consistent with Crohn's disease was used as the date of diagnosis.

Principles of management

The patients have been reviewed at least annually including clinical, biochemical and haematological assessment. Radiological examinations were performed in symptomatic patients and barium enema examination was particularly useful in identifying recurrent disease at anastomotic sites.

Disease activity

Disease activity was measured by changes in body weight. Serum orosomucoids were included from 1958 onwards. Serum albumin, haemoglobin and erythrocyte sedimentation rate were used throughout the study. Elevated serum orosomucoids and fall in serum albumin are of particular value in assessing colonic Crohn's disease activity.

Site of disease

The primary site of disease at diagnosis was right-sided (85 patients), left-sided or segmental (130 patients), or extensive (145 patients) colonic disease

The site of disease related to age at diagnosis is shown in *Figure 1*. Most patients over 60 years of age presented with left-sided colitis

Results

The results have been analysed in groups based on the primary site of disease at diagnosis.

Right-sided colonic involvement

All but ten of the 85 patients with right-sided disease also had macroscopic involvement of the adjacent distal ileum. Only nine patients (three men, six women) (11 per cent) have not required surgical treatment during the period of review and these patients have been followed for a mean of 13·5 years (range 4–32 years). All nine are currently alive and well, although three have developed extensive colitis during follow-up.

The most common indication for surgery in this group was obstructive symptoms. Other indications included abdominal abscess or fistula formation, general malaise, weight loss and diarrhoea. The mean interval between onset and surgery was 4 years (range 0–41 years). The cumulative operative rate with time from diagnosis among the patients undergoing resection is

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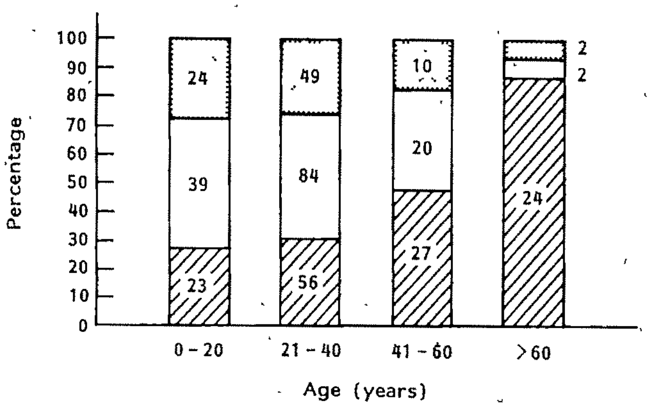

Figure 1 *Primary site of Crohn's colitis at diagnosis grouped according to age (percentage of total group and absolute numbers).* ⬚, *Right sided;* □, *extensive;* ■, *left colon*

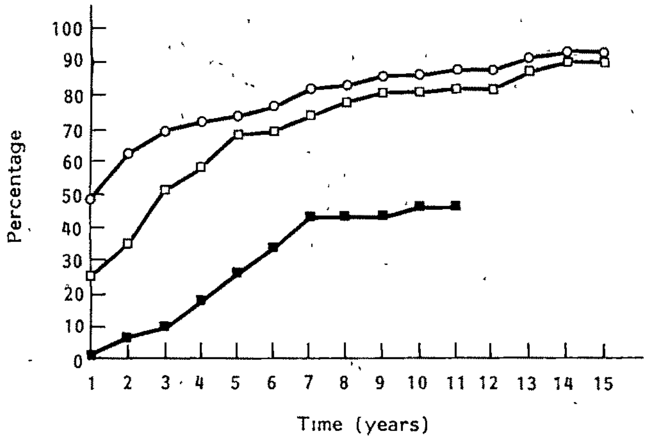

Figure 2 *Right-sided colonic disease. Cumulative operative rate from onset of symptoms* (□), *from diagnosis* (○), *and reoperative rate for recurrent disease after right hemicolectomy* (■)

shown in *Figure 2*. The cumulative operative rate was 35 per cent at 2 years, 68 per cent at 5 years and 81 per cent at 10 years from onset, and 62, 74 and 86 per cent respectively from diagnosis. The most common initial resection was right hemicolectomy (48), followed by colectomy and ileorectal anastomosis (12), bypass (five), panproctocolectomy (four) and others (seven). The surgical outcome in this group of patients is summarized in *Figure 3*. The cumulative reoperation rate for recurrent disease after right hemicolectomy is shown in *Figure 2*. The cumulative reoperation rate after right hemicolectomy at 2, 5 and 10 years was 7, 26 and 46 per cent respectively.

Left-sided disease

Of the 130 patients (60 men, 70 women) who presented with disease involving the sigmoid colon and/or rectum, 14 also had distal ileal involvement. Forty-nine patients (24 aged <40 years at diagnosis and 25 >40 years) had been treated without surgical treatment despite a mean follow-up of 8·2 years (range 0·1–42 years) from diagnosis. Of the 130 patients with left-sided disease, 81 (62 per cent) underwent resection after a mean interval of 6 years (range 0–25·2 years) from diagnosis. The main indications for surgery were persistent diarrhoea with general malaise, abscess or fistula formation, and troublesome perianal disease. In a few patients the initial resection was either of the distal ileum or right colon, where obstructive symptoms at this site were the major problem The cumulative operation rate from onset of symptoms to first operation and from diagnosis is shown in *Figure 4*. The operative rates from onset to first resection were 18 per cent at 2 years, 34 per cent at 5 years and 55 per cent at 10 years, and from diagnosis 36 per cent at 2 years, 53 per cent at 5 years and 67 per cent at 10 years.

The most common forms of surgical treatment were extensive resection involving either colectomy and ileorectal anastomosis, panproctocolectomy, colectomy and end ileostomy or segmental colectomy. The surgical treatment and outcome is summarized in *Figure 5*. Nearly half of the patients undergoing

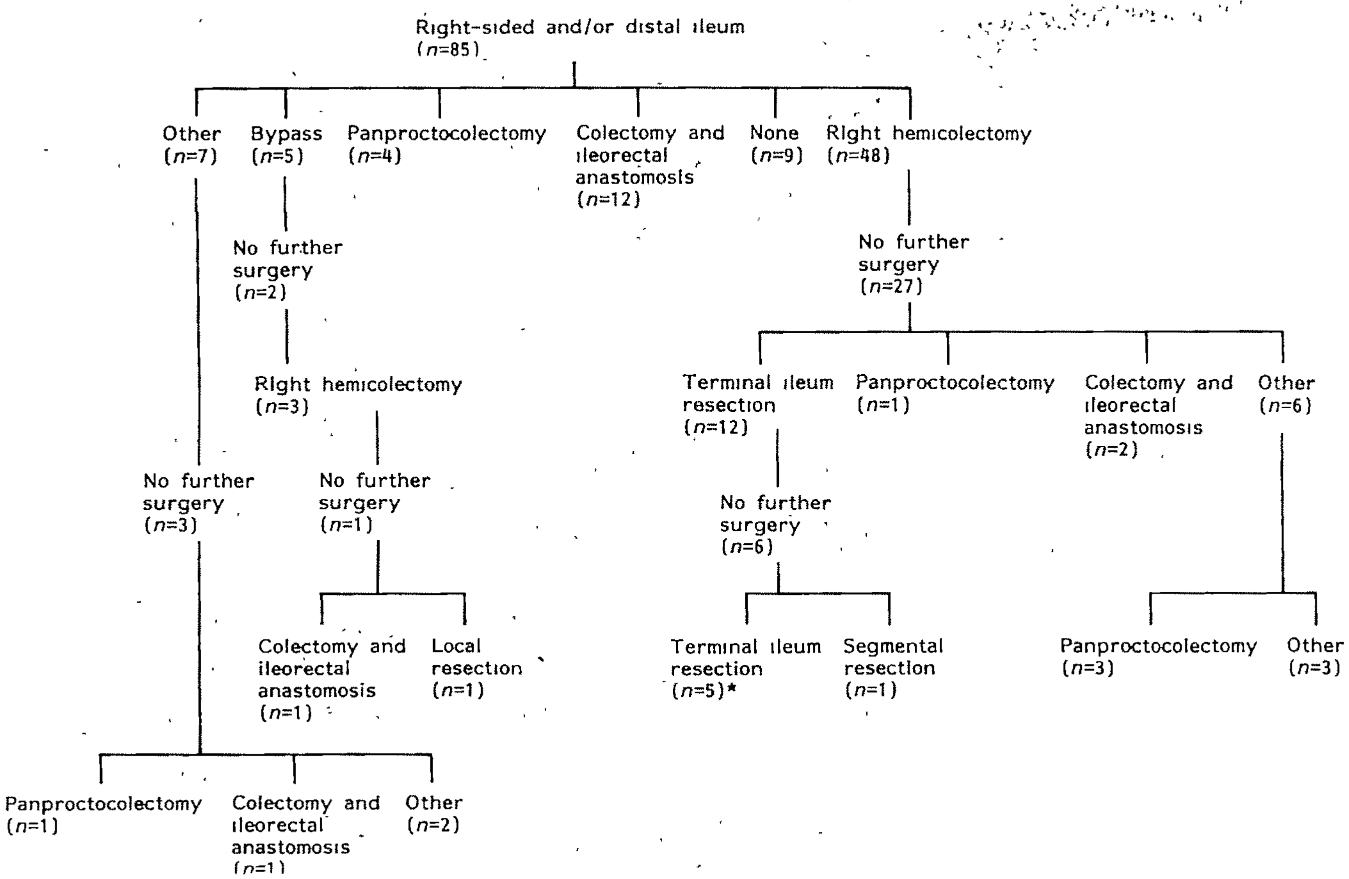
Right-sided and/or distal ileum (n=85)
Other (n=7)
Bypass (n=5)
Panproctocolectomy (n=4)
Colectomy and ileorectal anastomosis (n=12)
None (n=9)
Right hemicolectomy (n=48)
No further surgery (n=2)
No further surgery (n=27)
Right hemicolectomy (n=3)
Terminal ileum resection (n=12)
Panproctocolectomy (n=1)
Colectomy and ileorectal anastomosis (n=2)
Other (n=6)
No further surgery (n=3)
No further surgery (n=1)
No further surgery (n=6)
Colectomy and ileorectal anastomosis (n=1)
Local resection (n=1)
Terminal ileum resection (n=5)*
Segmental resection (n=1)
Panproctocolectomy (n=3)
Other (n=3)
Panproctocolectomy (n=1)
Colectomy and ileorectal anastomosis (n=1)
Other (n=2)

Figure 3 *Surgical management of right-sided colitis. * Three had further terminal ileum resection, of these, two had yet another terminal ileum resection. One patient had an ileostomy*

operation (36 of 81) had either colectomy alone ($n=10$), colectomy and ileorectal anastomosis or panproctocolectomy. Among these patients treated by either ileostomy alone or colectomy and end ileostomy, the majority eventually needed either excision of the colon or rectum. Further colonic resection was uncommon in those treated by segmental colectomy or resection of the distal ileum or right hemicolectomy, as appropriate.

Crohn's proctitis

Of the 130 patients with left-sided colitis, 44 had macroscopic disease confined to the rectum (23 aged <30 years and 18 >50 years). Most have been diagnosed since 1970 (31 of 44, 70 per cent). Crohn's proctitis may occur at any age but Crohn's disease diagnosed in the older patient is nearly always confined to the rectum or left colon. Because most of the older patients can be treated conservatively, the cumulative operative intervention rate is lower than in other groups (22, 29 and 33 per cent at 2, 5 and 8 years from diagnosis respectively; *Figure 6*).

Extensive colonic disease

Of the 145 patients (69 men, 76 women) who had extensive colonic involvement at diagnosis, 101 had distal ileal involvement. Thirty patients (18 women, 12 men) have run a relatively benign course without surgery despite a follow-up period from diagnosis of 10 years (range 0·6–28·25 years). One hundred and fifteen patients (79 per cent) with extensive colonic disease underwent surgical treatment. The cumulative operative rates from diagnosis to first resection are shown in *Figure 7*. The cumulative operative rates from onset were 20 per cent at 2 years, 41 per cent at 5 years and 63 per cent at 10 years, and from diagnosis were 35 per cent at 2 years, 56 per cent at 5 years and 74 per cent at 10 years. Eighty-seven of the 115 patients had an initial extensive colonic resection (colectomy and end ileostomy, colectomy and ileorectal anastomosis or panproctocolectomy) and a further 18 patients (105 of 115 patients in total) had extensive colonic resection during the period of follow-up. Of the ten patients initially undergoing ileostomy alone, seven were subsequently treated by colectomy. Seven of the 12 patients undergoing right hemicolectomy or terminal ileal resection eventually required colectomy (*Figures 8–10*).

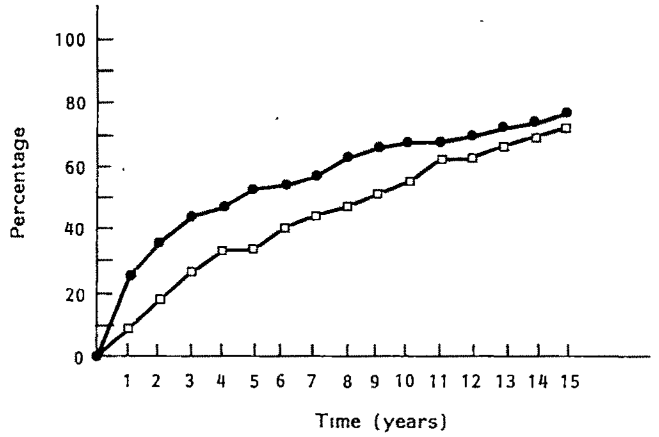

Figure 4 *Left-sided colonic Crohn's disease. Cumulative operative rates from onset of symptoms (□) and from diagnosis (●)*

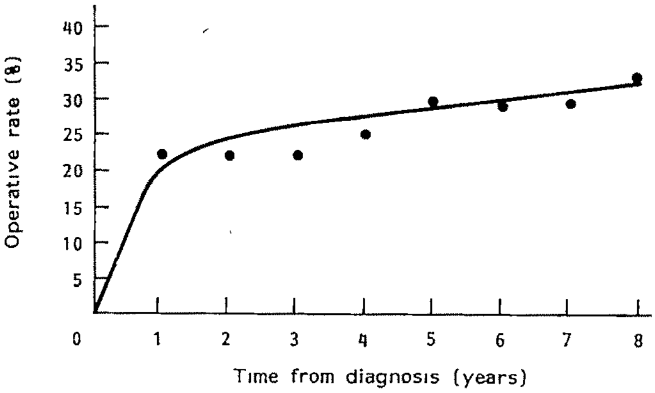

Figure 6 *Crohn's proctitis. Cumulative operative rate from diagnosis*

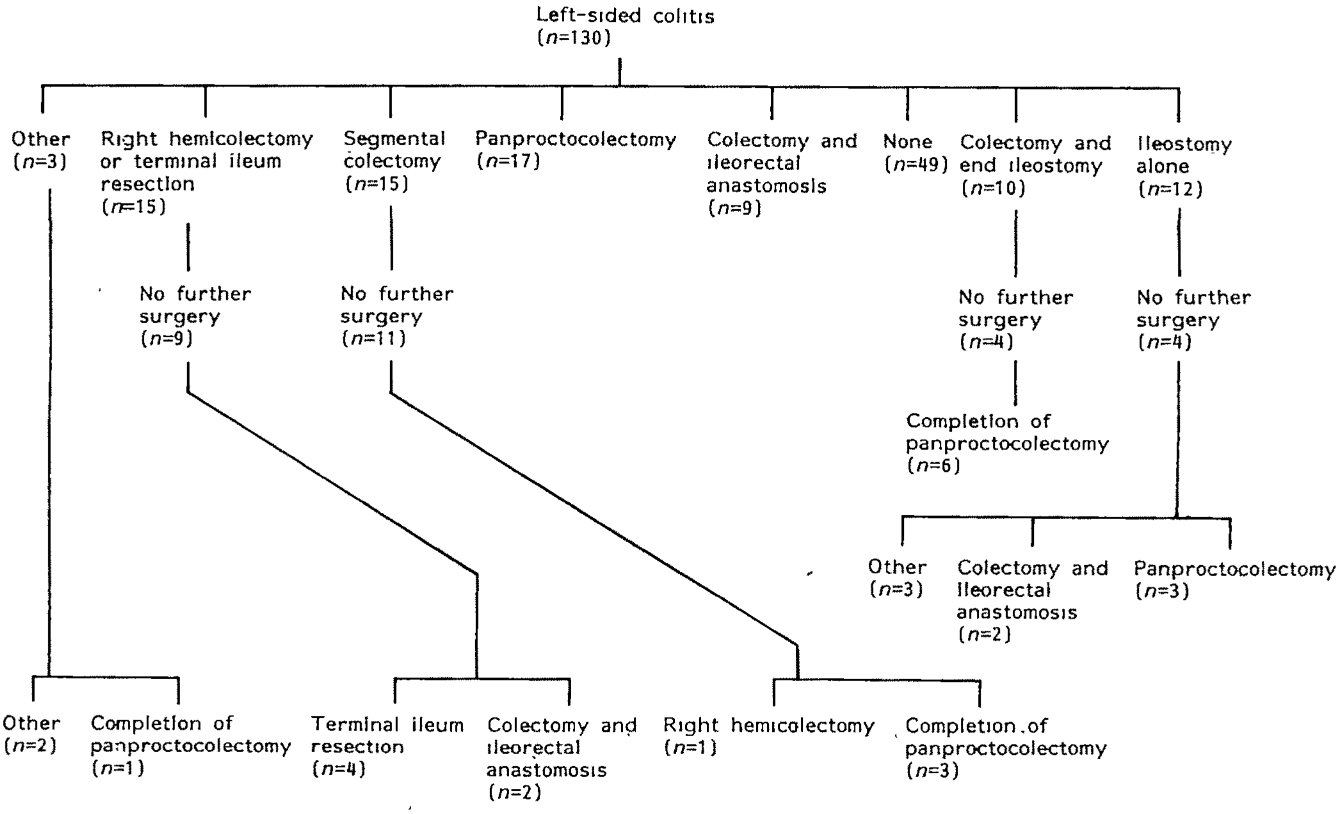
Left-sided colitis (n=130)
Other (n=3)
Right hemicolectomy or terminal ileum resection (n=15)
Segmental colectomy (n=15)
Panproctocolectomy (n=17)
Colectomy and ileorectal anastomosis (n=9)
None (n=49)
Colectomy and end ileostomy (n=10)
Ileostomy alone (n=12)
No further surgery (n=9)
No further surgery (n=11)
No further surgery (n=4)
No further surgery (n=4)
Completion of panproctocolectomy (n=6)
Other (n=3)
Colectomy and ileorectal anastomosis (n=2)
Panproctocolectomy (n=3)
Other (n=2)
Completion of panproctocolectomy (n=1)
Terminal ileum resection (n=4)
Colectomy and ileorectal anastomosis (n=2)
Right hemicolectomy (n=1)
Completion of panproctocolectomy (n=3)

Figure 5 *Surgical management of left-sided colitis*

Colectomy and ileorectal anastomosis for Crohn's colitis

The outcome after colectomy and ileorectal anastomosis for Crohn's colitis is summarized in *Figure 9*. Of the 80 patients, 68 underwent colectomy and ileorectal anastomosis as a primary resection and 12 for resection of recurrent disease. Nearly half the patients (35 of 80) have not undergone further resections despite a mean follow-up since colectomy and ileorectal anastomosis of 6·8 years (range 0·1–20·8 years). The most common indication for reoperation was recurrent disease proximal to the ileorectal anastomosis, followed by reactivation of disease in the rectum leading to proctectomy. Reoperation rates for recurrent disease after colectomy and ileorectal anastomosis was completed are shown in *Figure 11*. Cumulative reoperation rate at 2, 5 and 10 years was 27, 46 and 60 per cent respectively

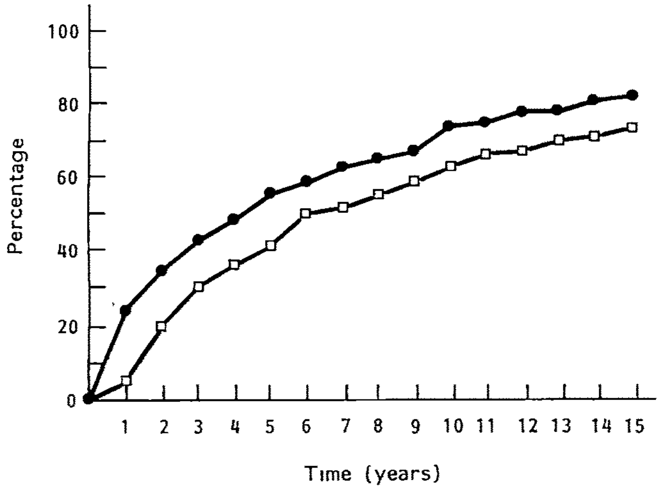

Figure 7 *Extensive colonic Crohn's disease. Cumulative operative rates from onset of symptoms* (□) *and from diagnosis* (●)

Outcome after panproctocolectomy for Crohn's disease

One hundred and ten patients have been treated by panproctocolectomy either as a primary procedure (48), for recurrent disease (39) or after colectomy and ileorectal anastomosis as a first (17) or subsequent (six) reoperation (*Figure 10*). Despite a mean follow-up period since panprocto-

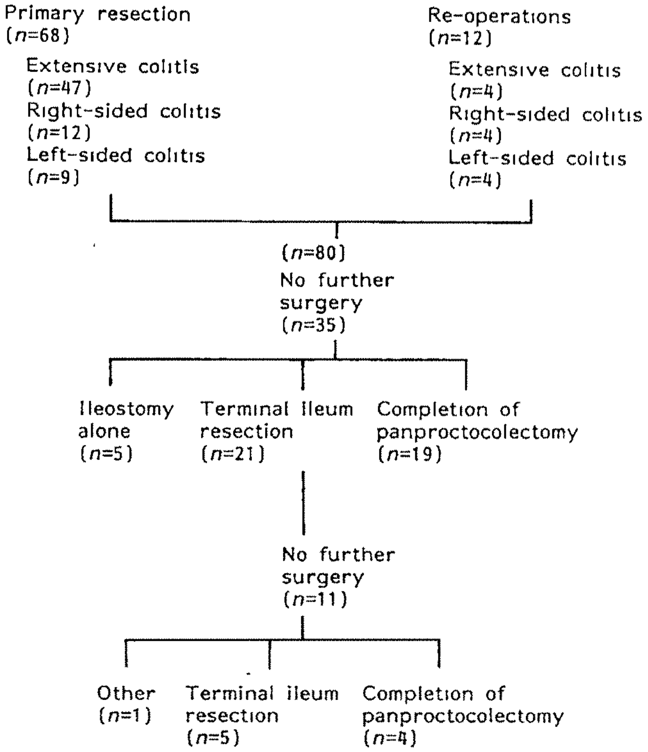
Primary resection (n=68)
Extensive colitis (n=47)
Right-sided colitis (n=12)
Left-sided colitis (n=9)
Re-operations (n=12)
Extensive colitis (n=4)
Right-sided colitis (n=4)
Left-sided colitis (n=4)
(n=80)
No further surgery (n=35)
Ileostomy alone (n=5)
Terminal ileum resection (n=21)
Completion of panproctocolectomy (n=19)
No further surgery (n=11)
Other (n=1)
Terminal ileum resection (n=5)
Completion of panproctocolectomy (n=4)

Figure 9 *Surgical outcome after colectomy and ileorectal anastomosis for Crohn's colitis*

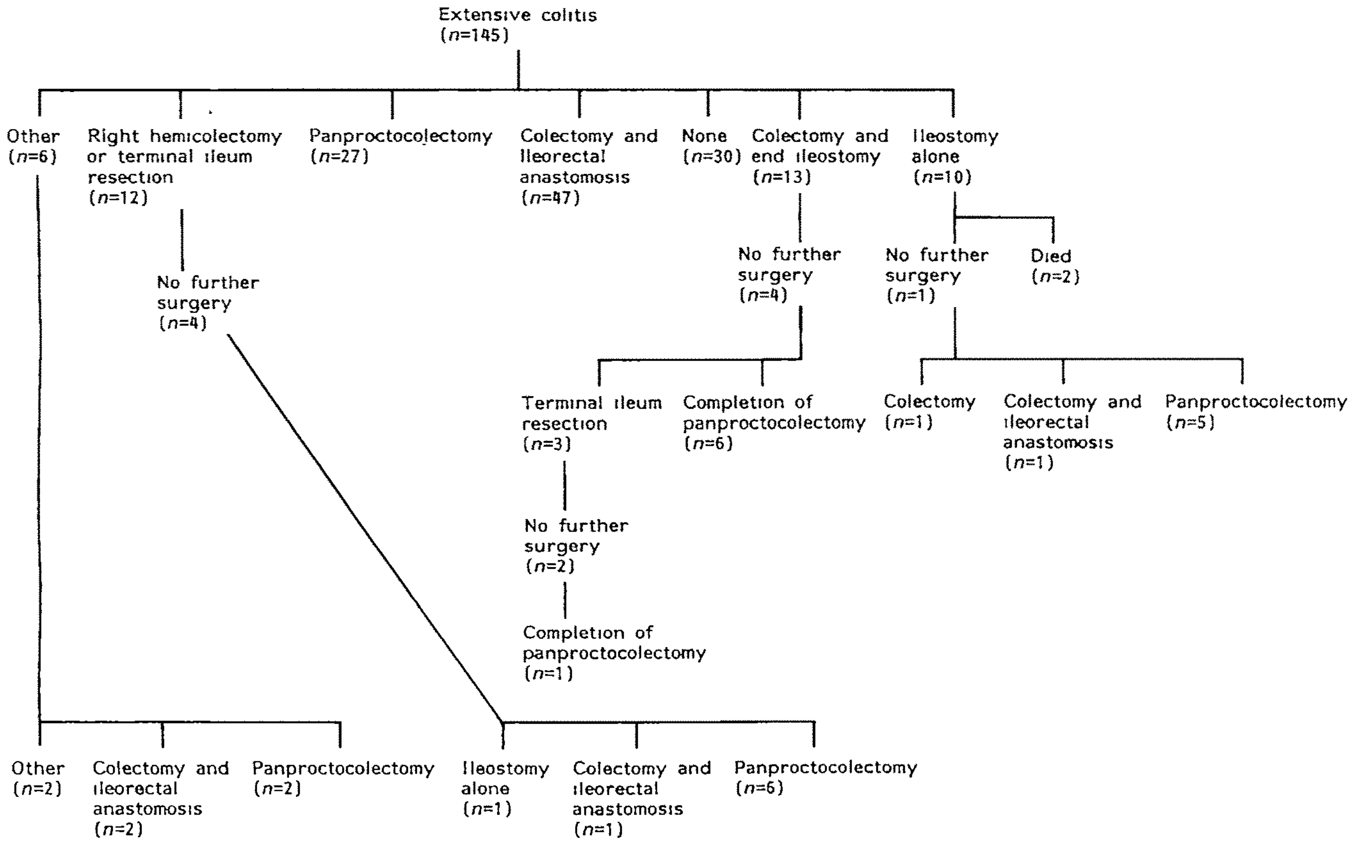
Extensive colitis (n=145)
Other (n=6)
Right hemicolectomy or terminal ileum resection (n=12)
Panproctocolectomy (n=27)
Colectomy and ileorectal anastomosis (n=47)
None (n=30)
Colectomy and end ileostomy (n=13)
Ileostomy alone (n=10)
No further surgery (n=4)
No further surgery (n=4)
No further surgery (n=1)
Died (n=2)
Terminal ileum resection (n=3)
Completion of panproctocolectomy (n=6)
Colectomy (n=1)
Colectomy and ileorectal anastomosis (n=1)
Panproctocolectomy (n=5)
No further surgery (n=2)
Completion of panproctocolectomy (n=1)
Other (n=2)
Colectomy and ileorectal anastomosis (n=2)
Panproctocolectomy (n=2)
Ileostomy alone (n=1)
Colectomy and ileorectal anastomosis (n=1)
Panproctocolectomy (n=6)

Figure 8 *Surgical management of extensive Crohn's colitis*

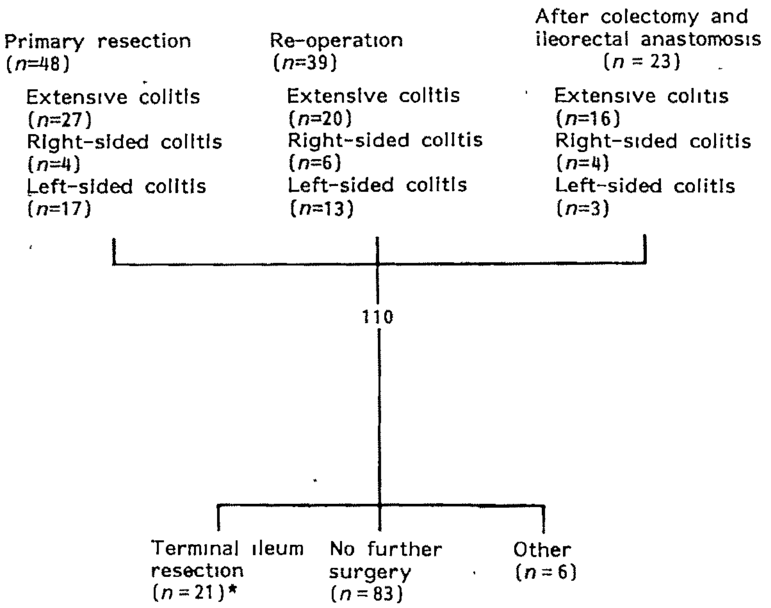
Primary resection (n=48)
Extensive colitis (n=27)
Right-sided colitis (n=4)
Left-sided colitis (n=17)
Re-operation (n=39)
Extensive colitis (n=20)
Right-sided colitis (n=6)
Left-sided colitis (n=13)
After colectomy and ileorectal anastomosis (n = 23)
Extensive colitis (n=16)
Right-sided colitis (n=4)
Left-sided colitis (n=3)
110
Terminal ileum resection (n = 21)*
No further surgery (n = 83)
Other (n = 6)

Figure 10 *Outcome after panproctocolectomy for Crohn's disease. * Two patients had further terminal ileum resections*

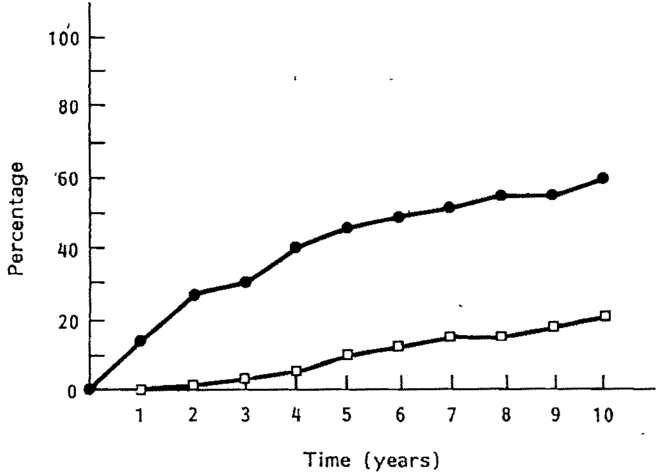

Figure 11 *Cumulative reoperation rates for recurrent disease after colectomy and ileorectal anastomosis* (●) *and after panproctocolectomy* (□)

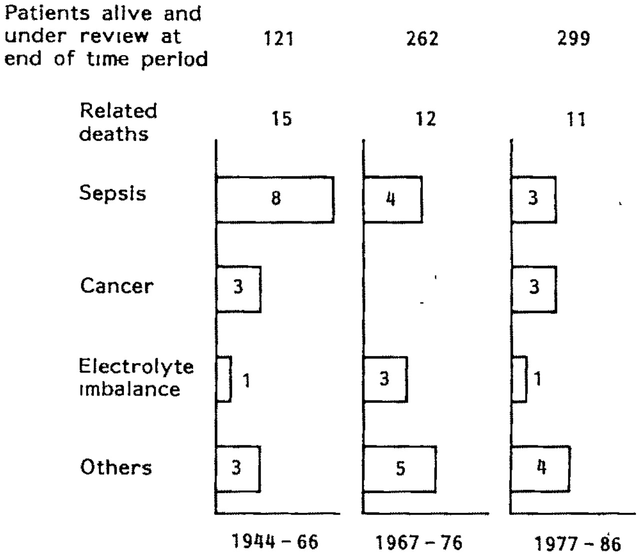

Figure 12 *Related deaths from Crohn's colitis*

colectomy of 8·2 years (range 0·2–30·1 years), 83 have not required further surgical treatment. The most common indication for reoperation is resection of recurrent disease in the distal ileum immediately proximal to the ileostomy. The cumulative reoperation rates after panproctocolectomy are shown in *Figure 11* and are 1, 10 and 21 per cent at 2, 5 and 10 years respectively.

Operative rates: primary and secondary referrals

The cumulative operative rate for patients referred from other hospitals is higher than among those patients in whom the diagnosis was made in this unit (64 *versus* 53 per cent at 5 years and 82 *versus* 62 per cent at 10 years).

Mortality

Of the 360 patients, 61 have died: 23 of unrelated causes. The 38 disease-related deaths are summarized in *Figure 12*. Despite the increasing number of patients under review there have only been 11 related deaths in the decade 1977–86, of which eight were probably unavoidable (*Figure 12*). The three potentially avoidable deaths were due to sepsis (two) and pulmonary embolus (one). Of the unavoidable deaths, three occurred from colorectal cancer complicating long standing colitis, one elderly woman presented with overwhelming sepsis, one 87-year-old patient presented with electrolyte imbalance and a decision was made not to undertake active treatment. One patient refused medical treatment and took corticosteroids at her own discretion, and one patient with chronic psychiatric problems was confined to bed and died of pulmonary embolus. The one remaining patient developed Takayasu's disease.

Current status

Of the 299 living patients, 285 are currently well (*Table 1*).

Right-sided disease. Of 85 patients with right-sided disease, 70 are alive. All nine patients treated conservatively are fit and well after a mean follow-up of 13·5 years, although three are known to have extensive colitis. Of 76 surgically treated patients, 58 are well, although 20 are known to have recurrent disease. Three are unwell and receiving corticosteroids (one has diffuse small bowel disease and two have total colitis). The duration of follow-up in the surgically treated group is 17 years (range 0·1–38·4 years).

Table 1 *Current status of 299 living patients*

Colonic disease	Management	Well	Well + corticosteroids	Unwell + corticosteroids
Right-sided	Conservative	9		
	Surgical	58		3
Left-sided	Conservative	42		1
	Surgical	65		4
Extensive	Conservative	24	1	
	Surgical	85	1	6
Total		283	2	14

Left-sided disease. Of 130 patients with left-sided disease, 112 are alive. Duration of follow-up was 8·2 years (range 0·1–42·7 years). Of the 49 treated conservatively, 43 are alive and all but one are well. Of the surgically treated group, duration of follow-up was 13·5 years (range 0·1–42·9 years); 69 of 81 are alive and all but four (who are taking corticosteroids) are well.

Extensive disease. Of 145 patients with total colitis, 117 are alive. Duration of follow-up was 10 years (range 0·6–28·2 years). All 25 survivors of the 30 patients treated conservatively are well and only one is taking steroids. Seven have total colitis of more than 10 years duration. Of the 115 surgically treated patients, 92 are alive and 86 are well (one on corticosteroids). Six are unwell and all are taking corticosteroids (*Table 1*). Duration of follow-up was 15·7 years (range 0·1–42·7 years).

Stoma patients. Of the total of 360 patients, 172 have had a stoma at some time (33 of 85 with right-sided, 50 of 130 with left-sided and 89 of 145 with extensive colonic disease). Of the 299 patients still alive, 122 have a stoma (14 with right-sided, 44 with left-sided and 64 with extensive colonic disease).

Discussion

This study of 360 patients under long-term review is biased towards the severely ill patient and contrasts with the epidemiological studies of Hellers[2] and Binder *et al.*[3]. It is, however, more representative of Crohn's colitis as seen in a hospital setting. The analysis has been mainly confined to the outcome after surgical treatment because the proportion of patients treated surgically will vary according to the nature and severity of symptoms among the patients studied.

Prolonged spontaneous or drug-induced remission occurred in all groups. The proportion among patients with right-sided disease was 11 per cent, extensive colonic disease 21 per cent and left-sided disease 38 per cent. These patients were not subject to prolonged or intensive therapy but probably represent a more benign end of the disease spectrum. Of the surgically treated patients most had either persistent symptoms amenable to surgical treatment (fibrous stricture, local abscess formation or enterocutaneous fistula) or symptoms which were not relieved by or had recurred following medical treatment, particularly general malaise, diarrhoea and weight loss.

In this series, after a mean interval from diagnosis of nearly 15 years, 76 per cent had undergone surgical treatment. Comparable figures of 39 per cent at 10 years were reported in a primary series from St. Mark's Hospital, London, UK of patients with Crohn's colitis seen between 1969 and 1973[4], and 55 per cent treated surgically after 10 years from diagnosis in an epidemiological study of Crohn's disease from Copenhagen[3].

Right-sided colonic disease

Symptoms in patients with right-sided colonic disease usually arise from the associated distal ileal involvement and the pattern of surgical intervention and reoperation rates are similar to those found in distal ileal disease[5]. The reoperation rates for recurrent disease following right hemicolectomy for right-sided colonic disease are 26 per cent at 5 years and 46 per cent at 10 years but, despite these relatively high reoperation rates, surgery is an effective way of restoring patients to good health – particularly those with short fibrous stricture.

Recurrent disease nearly always occurs at or around the anastomosis, resulting in clear-cut symptoms which, if they persist, can readily be resolved by further local resection. The outcome is unsatisfactory in a few patients where the disease, apparently confined to the right colon, initially recurs either diffusely in the small bowel or extensively in the colon, eventually requiring treatment by either colectomy and ileorectal anastomosis or panproctocolectomy (*Figure 3*). Bypass has only been undertaken in a few cases, its benefit is usually shortlived and most patients subsequently undergo resection.

Left-sided colonic disease

Although surgical treatment is not needed as commonly as in patients with extensive colitis, those patients who do warrant surgical intervention usually require either colectomy and ileorectal anastomosis or panproctocolectomy. Of patients treated initially by segmental resection most have subsequently required further surgery (*Figure 5*).

Crohn's proctitis

Patients with Crohn's disease confined to the rectum run a more benign course, predominantly because the older patient can usually be treated conservatively[6] and consequently surgical intervention rates are lower than at other sites (*Figure 6*).

Extensive colitis

Patients with extensive colitis at diagnosis can usually only be restored to good health by major surgical treatment. Ileostomy alone or segmental resection only temporarily improves symptoms (*Figure 8*).

When the rectum is spared or minimally involved, colectomy and ileorectal anastomosis is appropriate and nearly half the patients thus treated have not required further surgery despite a mean follow-up of 6 years. Nearly half of those requiring further surgical treatment had recurrent disease in the distal ileum which, after resection, enabled intestinal continuity to be restored.

Panproctocolectomy is particularly effective in restoring chronically ill patients to good health[7]; the risk of recurrent disease is small and is usually confined to the distal ileum immediately proximal to the stoma which is readily amenable to local resection if symptoms persist (*Figure 11*).

Acceptance of a permanent stoma is an integral part of management. Nearly half the patients (48 per cent) have required a stoma at some time during their management and, of the 299 patients still alive, 41 per cent have a permanent stoma. Most people with extensive Crohn's colitis will have persistent symptoms and prolonged ill health, and few are restored to good health without surgical intervention.

Mortality

A statistical study from this unit has demonstrated that deaths from Crohn's disease are twice as common as in the general population matched for age, sex and years at risk[8]. However, this overview conceals recent improvements. There have only been 11 related deaths in this series during the last decade, only three of which might have been classified as avoidable. This change in the pattern of mortality with time helps to explain the lower mortality observed in the recent series of Crohn's disease reported from Copenhagen[3].

Current status

Despite the high morbidity, the long-term prognosis is good as most patients are working full-time, undertaking housework or enjoying retirement. Currently only 14 have major symptoms and 16 are receiving specific medical treatment. Until the aetiology of Crohn's disease is identified, surgical treatment has an important and effective part to play in the overall management of patients with Crohn's disease.

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Construction of a neorectum and neoanal sphincter following previous proctocolectomy

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A new operation is described in which a neorectum and neoanal sphincter mechanism have been constructed to restore gastrointestinal continuity and continence in a patient who had previously undergone proctocolectomy and a permanent ileostomy. The neorectum was constructed by forming a triplicated pouch from the distal ileum. The neoanal sphincter was fashioned from a transposed gracilis muscle and was activated electrically by an implanted stimulator. A period of chronic low frequency stimulation altered the muscle characteristics and enabled the neosphincter to contract continually without fatigue. Complete continence was achieved by the neosphincter gripping a Silastic® plug inserted within the efferent spout of the pouch. The patient was able to void completely when the stimulator was switched off and the plug removed.

Keywords: Neorectum, electrically stimulated neoanal sphincter, protocolectomy

The surgical treatment for ulcerative colitis and familial adenomatous polyposis has been considerably improved in recent years by the introduction of mucosal proctectomy and pelvic pouch formation by Parks and Nicholls in 1978[1]. In this operation, all the diseased mucosa is removed by colectomy and rectal mucosectomy. Gastrointestinal continuity is restored by the creation of a pelvic ileal pouch which is sutured to the anal canal. Technical improvements have enabled most patients to have a reasonable bowel function, and the elimination of the ileostomy has enhanced the quality of their lives[2].

Despite this advance, there are patients with both ulcerative colitis and familial adenomatous polyposis in whom the operation fails or is contraindicated, and who by necessity must be left with a permanent ileostomy. In addition, there remain a considerable number of relatively young patients who have undergone proctocolectomy and ileostomy before the introduction of the pelvic pouch procedure. Whilst many of these patients remain satisfied with their ileostomy, a substantial proportion do not.

The dissatisfaction of one of our ileostomy patients led us to devise a new procedure, the purpose of which was to restore gastrointestinal continuity and continence by the construction of both a neorectum and a neoanal sphincter. The neorectum consisted of a pelvic ileal pouch and the neoanal sphincter was constructed from a transposed gracilis muscle[3], which was continually stimulated electrically by an implanted stimulator.

Patient and methods

A 29-year-old man first presented to The London Hosptal in 1986 requesting reversal of his ileostomy. His mother died of carcinoma of the colon at the age of 27 years and he was diagnosed as having familial adenomatous polyposis after a screening colonoscopy and, at the age of 18 years, underwent colectomy and ileorectal anastomosis. After this procedure his bowel function was acceptable but he developed numerous polyps in the rectal stump, many of which showed dysplastic change. It was not possible to control these with diathermy fulguration and in 1983 he underwent rectal excision and a Brooke end ileostomy. After this procedure, he never came to terms with his ileostomy and requested numerous opinions seeking reversal of the ileostomy.

Clinical examination revealed a fit young man with a healthy end ileostomy. The perineal wound was well healed and there was no sinus. Attempted voluntary contraction of the perineal region showed normal gluteal contraction but suggested the absence of the external anal sphincter and puborectalis muscles. The latter was confirmed by electromyographic examination. A small bowel meal showed no evidence of polyps. The new procedure together with the risks were fully explained to the patient and in April 1988 he underwent the first stage of the operation.

Operative technique

Stage 1. A laparotomy was performed with the patient in the modified Lloyd-Davies position and the ileostomy was mobilized from the abdominal wall. The small bowel was fully mobilized up to the root of the mesentery where the superior mesenteric vessels exit from above the third part of the duodenum. After ensuring that the distal 40–50 cm of ileum would reach the perineum, a triplicated ileal pouch (15 cm limbs) with a 1-cm efferent spout was manually constructed in two layers[1]. The pelvic dissection was then commenced and the ureters were identified, mobilized and preserved. The posterior wall of the bladder was identified and both this and the prostrate were mobilized and retracted anteriorly. The levatores ani were identified and cleared of debris and scar tissue. The junction of the two muscles was identified in the midline and a track was then created downwards between the muscles towards the perineal skin.

Via a perineal approach, a disc of skin and underlying fibrous tissue measuring about 2 cm in diameter was removed from the central part of the perineal scar. The dissection continued upwards to meet the tunnel previously created in the abdomen. This track was enlarged by manual stretching.

The ileal pouch was drawn down through the pelvic tunnel taking great care to ensure its correct orientation. The efferent spout was sutured circumferentially to the perineal skin using interrupted 3/0 Vicryl® sutures (Ethicon Ltd, Edinburgh, UK) (*Figure 1*). A covering loop ileostomy was then constructed about 20 cm proximal to the pouch. The postoperative course was uneventful and 4 weeks after the first procedure the second stage was performed.

Stage 2. With the patient in the modified Lloyd-Davies position a longitudinal incision was made in the left thigh. The left gracilis muscle was identified and mobilized down to its insertion into the tibial tuberosity. The tendon was divided and the proximal part of the muscle was fully mobilized[3] during which the neurovascular bundle was identified, using a nerve stimulator, where it entered the lateral border of the muscle in its proximal one-third. The principal nerve to the muscle was traced on to the lateral surface of the muscle. An electrode plate (Medtronic Resume, Medtronic Inc., Minneapolis, USA) containing four platinum–iridium electrodes was positioned over the main trunk of the nerve and its branches (*Figure 2*). The position of the electrodes was adjusted until a point was found where the voltage threshold for the contraction of the whole of the muscle was at its lowest (c. 2·0 V, 0·2 ms pulse at 1 pulse/second). When this position was located the electrode plate was sutured into position with interrupted fine silk sutures, taking care

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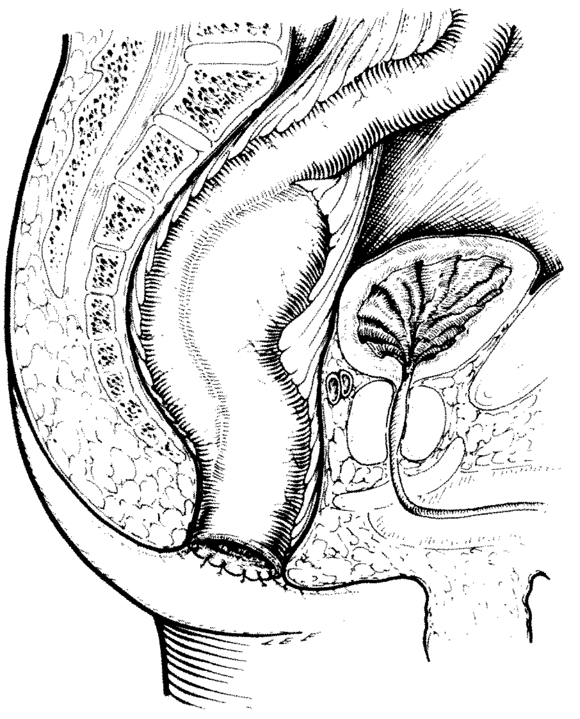

Figure 1 *Stage 1: a triplicated ileal pouch was made and anastomosed to the perineal skin. A loop ileostomy (not shown) was constructed about 20–30 cm proximal to the pouch*

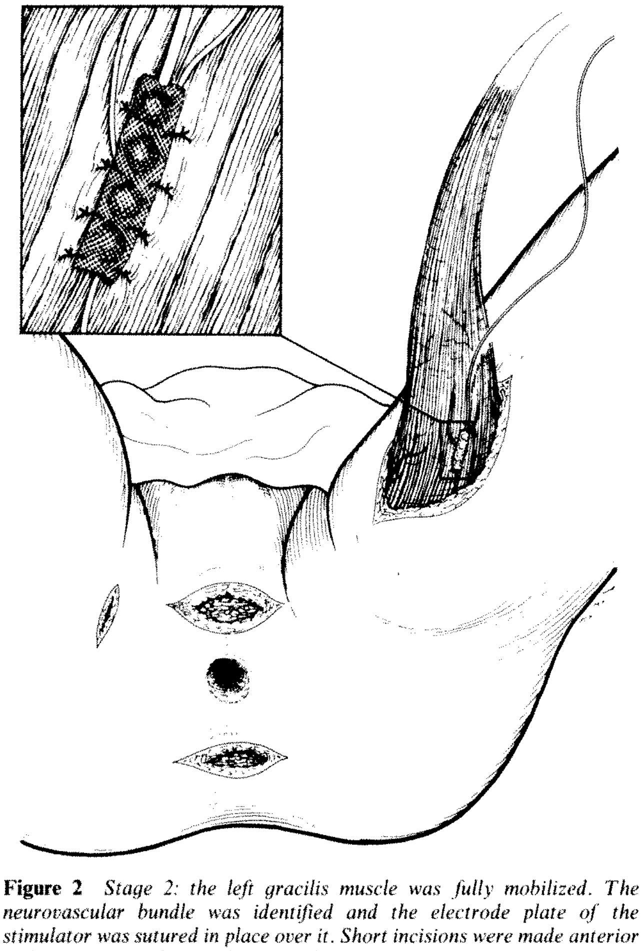

Figure 2 *Stage 2: the left gracilis muscle was fully mobilized. The neurovascular bundle was identified and the electrode plate of the stimulator was sutured in place over it. Short incisions were made anterior and posterior to the pouch–perineal anastomosis*

not to damage the nerve or blood supply of the muscle. Two 1–2 cm curvilinear incisions were then made anteriorly and posteriorly in the perineal skin about 1·5 cm from the ileoperineal anastomosis (*Figure 2*). A circumferential subcutaneous tunnel was created around the efferent spout of the pouch subcutaneously and the gracilis muscle was drawn down from the thigh and passed in a clockwise direction around the neoanal canal (*Figure 3*). The tendon of the muscle was sutured to the opposite ischial tuberosity with the left leg adducted so that the muscle sling was tightly applied around the neoanal canal. The muscle was stimulated once again to ensure that it produced an adequate contraction capable of occluding the anal canal. The stimulator wires were connected to the receiver of a Medronic 3522A (Medtronic Inc.) stimulator (*Figure 3*). The receiver was positioned in a subcutaneous pocket overlying the 8–9th ribs in the midclavicular line.

Postoperative course and physiological investigations

The patient was confined to bed for 5 days with both legs adducted. His recovery was uneventful and, after the 5th postoperative day, he was gradually mobilized, being discharged home on the 7th postoperative day. One month after discharge he was investigated in the anorectal physiology laboratory. The Medtronic 3522A was used to activate the receiver and stimulate the muscle. A Gaeltec (Gaeltec Ltd, Dunvegan, Isle of Skye, UK) microtransducer pressure probe within the neoanal canal was used to record sphincter contraction. The stimulator output voltage and frequency were increased until a fused tetanic contraction was elicited. The minimum stimulus frequency which resulted in a fused tetanic contraction was about 25 pulses per second. After an initial short peak, the pressure in the neoanal canal fell to a plateau which was maintained for 2 min. A saline stress test was performed by infusing physiological saline at a rate of 77 ml/min through a catheter placed in the neorectum. Without stimulation, leakage occurred after the infusion of 32 ml. With tetanic activation of the neosphincter, leakage occurred after 45 ml.

The patient was instructed to use the stimulator for 24 h per day at a frequency of 2 pulses per second and at a voltage that elicited a perceived

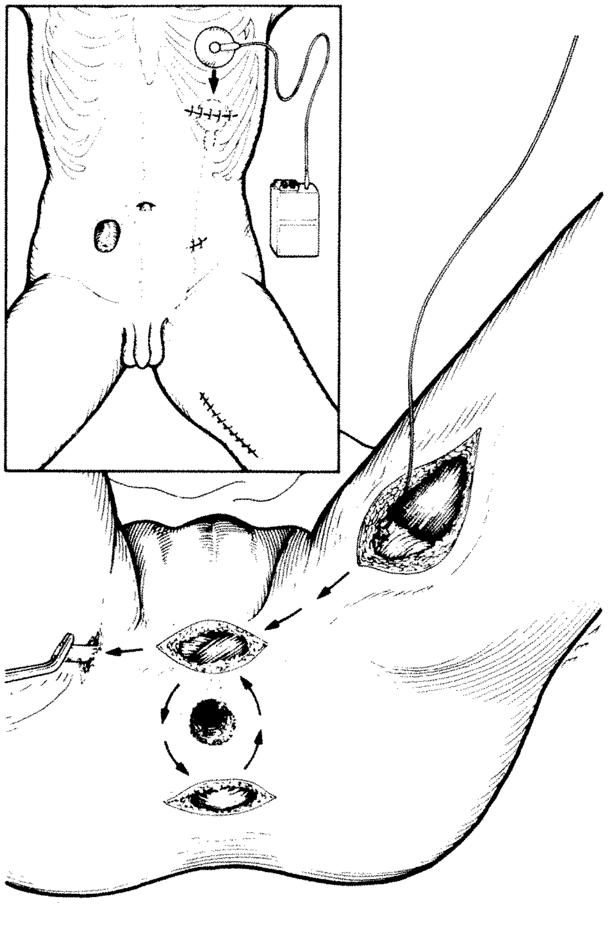

Figure 3 *Stage 2: the gracilis tendon was drawn down and round the efferent spout of the ileal pouch and sutured to the right ischial tuberosity so that when stimulated the 'neoanal canal' was occluded. Inset: the stimulator wires were connected to the receiver of the stimulator which was positioned in a subcutaneous pocket overlying the 8th and 9th ribs anteriorly. The transposed muscle was stimulated by positioning the transmitting aerial of the external stimulator over the receiver. Note the covering ileostomy which was closed 2 months after Stage 2*

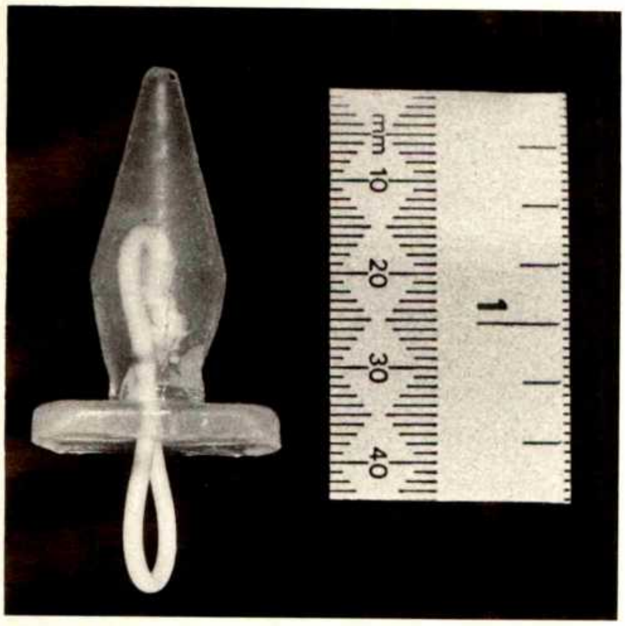

Figure 4 *The Silastic® plug, which was inserted into the neoanal canal and on which the neoanal sphincter contracted to produce continence*

contraction. After 6 weeks of continual stimulation it was found that the muscle was only contracting intermittently. The fault was localized to the electrodes on the neuromuscular bundle. A re-exploration of the electrode site was performed. It was found that part of the electrode plate had come away from its original position. The electrode was repositioned and sutured in place. The patient made an uneventful recovery and continual low frequency stimulation was recommenced on the 6th postoperative day.

Six weeks after the re-exploration he was reinvestigated. The fusion frequency was now 18 pulses per second and the pressure plateau was maintained for 24 min. Leakage occurred after the infusion of 23 ml of saline into the neorectum without sphincter activation, but with tetanic sphincter activation leakage occurred after the infusion of 90 ml. The decrease in the fusion frequency, the increase in duration of the plateau of pressure increase and the increase in volume to leakage during the saline stress test suggested that conversion from rapid twitch to slow twitch muscle had commenced.

The continence mechanism was also tested using a semisolid synthetic 'stool' consisting of oatmeal, barium sulphate and water[4]. When 120 ml of this stool was infused into the pelvic pouch a feeling of fullness was produced. The patient was allowed to be ambulant, but some leakage of stool occurred. As a result, a Silastic® (Dow Company, Reading, UK) 'plug' was devised (*Figure 4*) that fitted into the neoanal canal so that when the stimulator was turned to a subtetanic frequency the neosphincter gripped the plug and it could not be withdrawn easily. The patient was tested again with artificial stool. The plug remained in place overnight for a 16-h period; total continence was achieved throughout the period. The ileostomy was then closed.

Result

Two days after ileostomy closure the patient passed ileal fluid through the neoanal canal. The plug was then inserted and the patient was instructed to use the stimulator for periods of 2 h, after which it was switched off and the pouch evacuated. The patient was able to void spontaneously and empty the pouch completely after the stimulator was switched off and the plug removed. The interval during which the stimulator remained on continually was gradually increased until evacuation was only performed 4–6 times per day. The patient did not experience any discomfort from the presence of the plug which he was able to easily remove and insert at will when the stimulator was switched off.

Three weeks after ileostomy closure he developed small bowel obstruction which did not respond to conservative measures. A laparotomy was performed and an adhesion which had caused a volvulus of the proximal jejunum was found and divided. He made a rapid recovery from this procedure and the above regimen was reinstituted. He was discharged home 14 days after the laparotomy and was fully continent, evacuating the pouch 2–3 times per 24 h. This situation was maintained for 3 months. However, during this period he developed extensive perianal warts which had been a problem in the past. He found it increasingly difficult to insert the silastic plug. This eventually resulted in faecal seepage, his perineal warts became very inflamed and a defunctioning loop ileostomy was re-established. The patient requests that this is closed once the warts have been successfully treated.

Discussion

In this paper we report for the first time a procedure which reconstructs both a neoanorectum and neoanal sphincter mechanism in a patient who had previously undergone proctocolectomy. We have shown that the operation is feasible; the patient was continent and able to void spontaneously, provided the stimulator was turned off and the plug removed. The reconstruction of a new anorectal mechanism required various factors to be fulfilled. The loss of the rectum means there is no storage organ. This was the reason that Valiente and Bacon[5] first in animals, and then Parks and Nicholls[1] in man, constructed an ileal pouch in the original operation of restorative proctocolectomy. We have taken this factor into account and used a triplicated pouch with a short efferent spout of 1·0 cm to replace the rectum. The short length of the spout was considered important as a longer efferent limb may have prevented spontaneous evacuation[6]. Unlike both Parks and Nicholls and Valiente and Bacon, we had to anastomose our neorectum to the perineal skin and not the anal canal.

In order to replace the anal sphincter it is necessary to have a structure which possesses resting tone and is able to mount a sustained maximum contraction capable of resisting intra-abdominal pressure. In addition, such a neosphincter needs to retain its ability to dilate and stretch so that evacuation can proceed. Previous work in animals had suggested that chronic low frequency electrical stimulation of rapid twitch muscle would convert it to a slow twitch muscle[7,8]. We surmised, therefore, that when this was applied to the transposed human gracilis its subsequent conversion would enable it to function as a sphincter. In a series of animal studies[9] we showed that this could be achieved, and in the present patient these results were confirmed. After 6 weeks of low frequency stimulation the neosphincter fusion frequency was decreased as shown by our physiological tests, suggesting that conversion of rapid twitch to slow twitch muscle had commenced. As a result, the neosphincter was able to maintain sufficient tone for it to grip the intra-anal plug for a long period of time without fatigue, provided the stimulus remained subtetanic. Even without the plug, a maximum tetanic contraction occluded the anal canal completely but fatigue intervened after several minutes and some leakage occurred. After the stimulus ceased and the plug was removed the muscle relaxed sufficiently to allow complete evacuation to occur. It might be expected that in the absence of the entire anorectum the patient would experience no sensation of impending defaecation. This was not the case; the desire to defaecate, although not entirely normal, was experienced by the patient as a sense of fullness in the lower abdomen. Whether this sensation was mediated through receptors which are believed to be present in the muscles of the pelvic floor can only be surmised[10,11]. Despite some sensation being present, discrimination of flatus and faeces was not possible. This is hardly surprising as the sensitive anal canal mucosa was entirely replaced by the relatively crude ileal mucosa, which lacks the specialized sensory apparatus present in the normal anal canal[12].

We would stress that the operation has been developed by a multidisciplinary team, including a neurophysiologist and neurosurgeon, both of whom had extensive previous experience with the neurostimulator[13]. This we regard as a prerequisite for the progress achieved. Whilst the patient ultimately needed a defunctioning ileostomy he remained completely continent for 3 months. The ileostomy was required because he developed severe perianal warts which prevented satisfactory insertion of the Silastic plug. The substantial improvement in the patient's lifestyle before this complication was underlined by his desire to have the stoma closed once the warts are eradicated. Clearly this is a technique which needs further development. The purpose of this report is to demonstrate the feasibility of the procedure. Many questions need to be answered before it could become more widespread. We have to determine its reproducibility, its indications, and its long-term reliability. The stability of the electrode placement must be determined. Sepsis might be considered a potential problem because this has marred the success of other procedures which have relied on the implantation of foreign material to treat incontinence. As all the foreign material in our procedure is implanted well away from the perineum, and provided strict asepsis is adhered to during the perioperative period, we do not envisage any greater sepsis rates than those achieved with the implantation of cardiac pacemakers and stimulators used for pain.

We believe that the technique may in the future be an alternative for those patients with ulcerative colitis and familial adenomatous polyposis who have or require a permanent ileostomy, and are unsuitable for conventional restorative proctocolectomy. It it also obvious that a similar technique could be applied to selected patients who have had or require an abdominoperineal excision of the rectum for whatever reason. Similarly, the stimulated transposed gracilis when used alone could restore continence in incontinent patients who have an intact but deficient anal sphincter and in whom a conventional operation has failed or is not indicated. Indeed the latter appears to be the case from our initial data[14].

It must be pointed out that the procedure described is not without risk. If failure occurs the pouch may have to be dispensed with and the patient would lose 40–60 cm of terminal ileum with the concomitant problems associated with that loss. This complication is, however, also applicable to conventional restorative proctocolectomy. Nevertheless, our patient suffered some morbidity, and, whilst we are confident this can be reduced in future, the operation can only be offered at present to highly motivated individuals. Despite the problems we believe that this procedure could eventually eliminate the need for permanent stomas for the majority of patients.

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Functional closure of the femoral canal revealed by computed tomographic scanning

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The lacuna vasorum contains, as well as the external iliac vessels, a space called the femoral canal which allows pulsation and other changes in the diameter of the two vessels. The canal is closed by a connective tissue septum which is too weak to prevent a herniation alongside the vessels. The functional closure of the canal was investigated by artificial augmentation of the intraluminal pressure of the vein in five specimens and by computed tomographic (CT) scanning during a Valsalva manoeuvre in ten normal persons. In the abdomen the intraluminal and extraluminal pressures are raised in parallel, with no consequence for the diameter of the vessels. In the area of the lacuna vasorum the intravenous pressure is conveyed down to the first competent valve which is located 0·5 cm distal to the inguinal ligament, while the extraluminal pressure is reduced to normal. At each rise of the intra-abdominal pressure the vein will therefore bulge and exactly fill the empty space of the femoral canal thus preventing herniations by an on-demand mechanism. By CT scanning it was found that the vein in the femoral canal increased its diameter 2·5–3·0 times during the Valsalva manoeuvre.

Keywords: Canalis femoralis, hernia, computed tomographic scanning, functional anatomy

The abdominal cavity is a pressure area, out of which several openings lead. At each opening there is a mechanical problem of allowing free passage for the normal content of the canal on desired occasions without letting unwanted content or structures pass through or herniate alongside.

The mechanical problem is different at each site depending on the functional demands, and active sphincters as well as passive mechanisms are employed. The sites where vessels enter or leave the abdominal cavity are guarded by passive mechanisms, for example the hiatus of the aorta and the inguinal canal, with its pampiniform plexus, are closed primarily by their oblique course through the abdominal wall, while the foramen of the inferior vena cava is secured by adherence of the central tendon of the diaphragm to the periphery of the vein.

The external iliac artery and vein are large vessels which leave the abdominal cavity at a right angle to the abdominal wall and with ample room around them in the femoral sheath. The vessels are located in a common sheath which medially contains a space, the femoral canal. The canal is filled with areolar tissue and lymphatics, thereby allowing changes in the diameter of the two vessels within the limits of the sheath[1–3]. The abdominal end of this canal is covered by a delicate septum, a continuation of the fascia transversalis, but this alone can barely resist the intra-abdominal pressure[3]. The mechanism by which herniation at this site is resisted is unexplained.

With the first competent valve of the venous system of the leg located at the inguinal ligament just outside the abdominal pressure area[4], the mechanism of closure could be that the vein becomes distended by increased abdominal pressure and thereby exactly fills the canal, closing it when necessary. The soft tissues in question are structurally defined well enough to be outlined by computed tomographic (CT) scanning, and it was decided to combine an investigation on autopsy material with functional *in vivo* tests performed with the CT scanner.

Materials and methods

The external iliac and femoral veins were studied in five cadavers at autopsy. The inguinal ligament and the inner ring structures of the femoral canal were left untouched. Through a cannula connected to a pressure gauge, saline was injected into the external iliac vein under a pressure of 80–100 mmHg, which is comparable to the intra-abdominal pressure during a cough or straining manoeuvre. The enlargement of the vein was measured, and the fullness of the femoral canal was registered with a probe before and after applying the pressure.

The veins were then excised, and histological sections were made of sectors located proximally, deep to, and distally to the inguinal ligament. The sections were stained with haematoxylin and eosin, and for elastin and collagen fibres.

The experiment on the vein was repeated with CT scanning on ten living subjects who had given their informed consent. The subjects had normal inguinal regions. There were five men and five women aged 30–40 years. Two scans were made of each person in the supine position, one scan during quiet breathing and one during a Valsalva manoeuvre where a high intra-abdominal pressure was established for approximately 20 s. In one case longitudinal scans through the vein were constructed by the computer from 15 transverse sections separated by 5-mm intervals.

Results

In each of the five cadavers the first competent valve in the femoral vein was located 0·5 cm distal to the inguinal ligament. The wall immediately proximal to the valve, the so-called sinus of the valve, was thin and lacked a substantial tunica intima and media, which otherwise are pronounced in the iliac and femoral veins. When the pressure was applied to the vein the sinus was enlarged like a bulb sufficient in size to occupy the free space of the femoral canal without impinging on its margins. No space then remained in the canal alongside the vein (*Figures 1a* and *1b*).

By CT scanning, the content as well as the limits of the femoral sheath were clearly demonstrated (*Figure 2*). During the Valsalva manoeuvre the vein deep to the inguinal ligament increased its diameter from approximately 6 × 9 mm to 10 × 15 mm. The cross-sectional area was thereby increased 2·5–3·0 times, and it was found that the vein was able exactly to fill out the available space in these *in vivo* situations (*Figure 2b*). In three cases no enlargement was found, probably because of unsuccessful co-operation during the moment of radiography.

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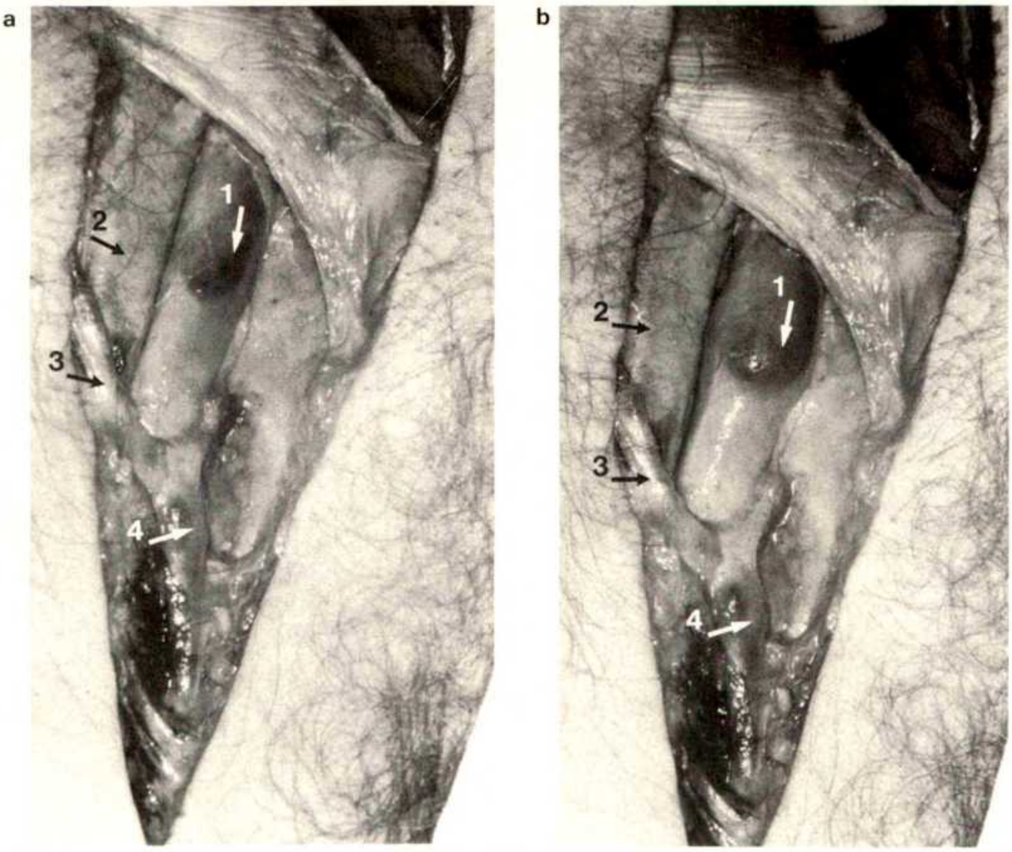

Figure 1 *Frontal sections* **a** *Right femoral vein (1) and artery (2) emerging under the inguinal ligament in autopsy specimen.* **b** *When a pressure of 80–100 mmHg is applied to the external iliac vein, the sinus proximal to the venous valve expands and occupies the empty space in the femoral canal; 3, superficial circumflex iliac vein; 4, great saphenous vein*

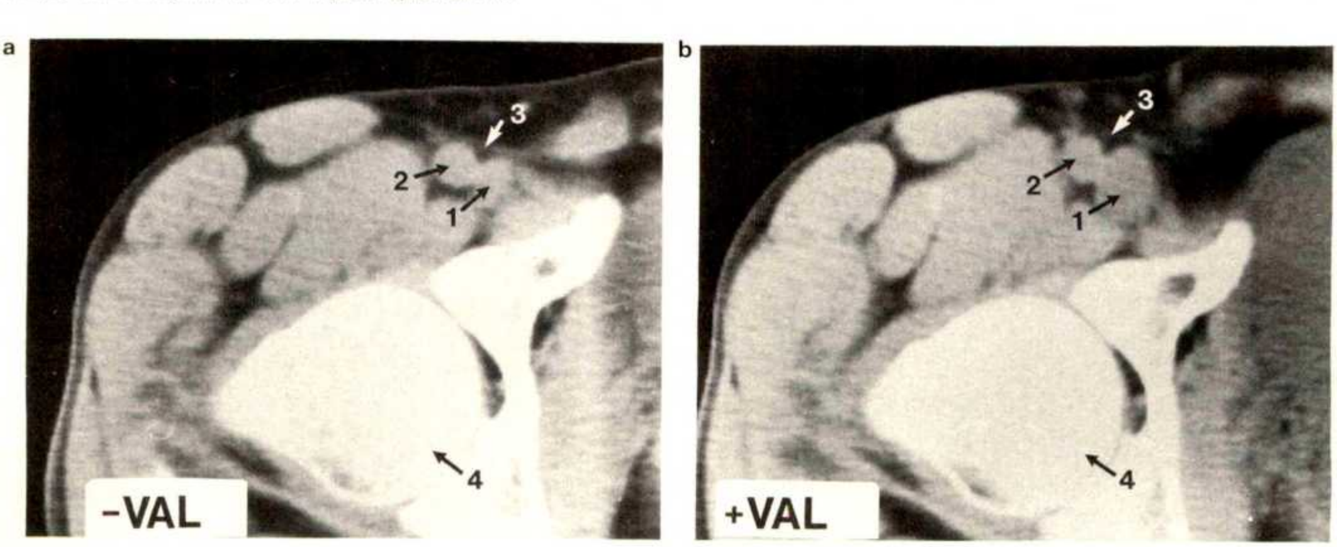

Figure 2 *Transverse computed tomographic scans at the inguinal ligament showing the increase in the trans-sectional area of the vein (1)* **a** *from quiet breathing* **b** *to the Valsalva manoeuvre. During the latter the vein creates a functional closure of the femoral canal; 2, femoral artery; 3, inguinal ligament; 4, head of femur*

From the constructed longitudinal scans the one through the middle of the vein was selected (*Figure 3*). This also showed the enlargement of the vessel at its transition from intra-abdominal to extra-abdominal position.

Discussion

The femoral sheath is unique in letting its content, the femoral artery and vein, pass through the abdominal wall at a right angle to the wall, with ample room alongside and with no sphincter muscle to close it off. The femoral septum which covers the internal ring is delicate and has no fascial back-up to carry the pressure as in the inguinal region, where the fascia transversalis is supported anteriorly by the external oblique aponeurosis.

The present investigation shows that the part of the vein that lies deep to the inguinal ligament expands its cross-section at each rise in intra-abdominal pressure enabling it exactly to occupy the funnel-shaped femoral sheath. The inner ring of the femoral canal is thus closed off by an on-demand mechanism, and the role of the septum seems more to be a curtain that can be drawn aside.

While the diameter of the intra-abdominal veins is almost constant because the intraluminal pressure follows the pressure

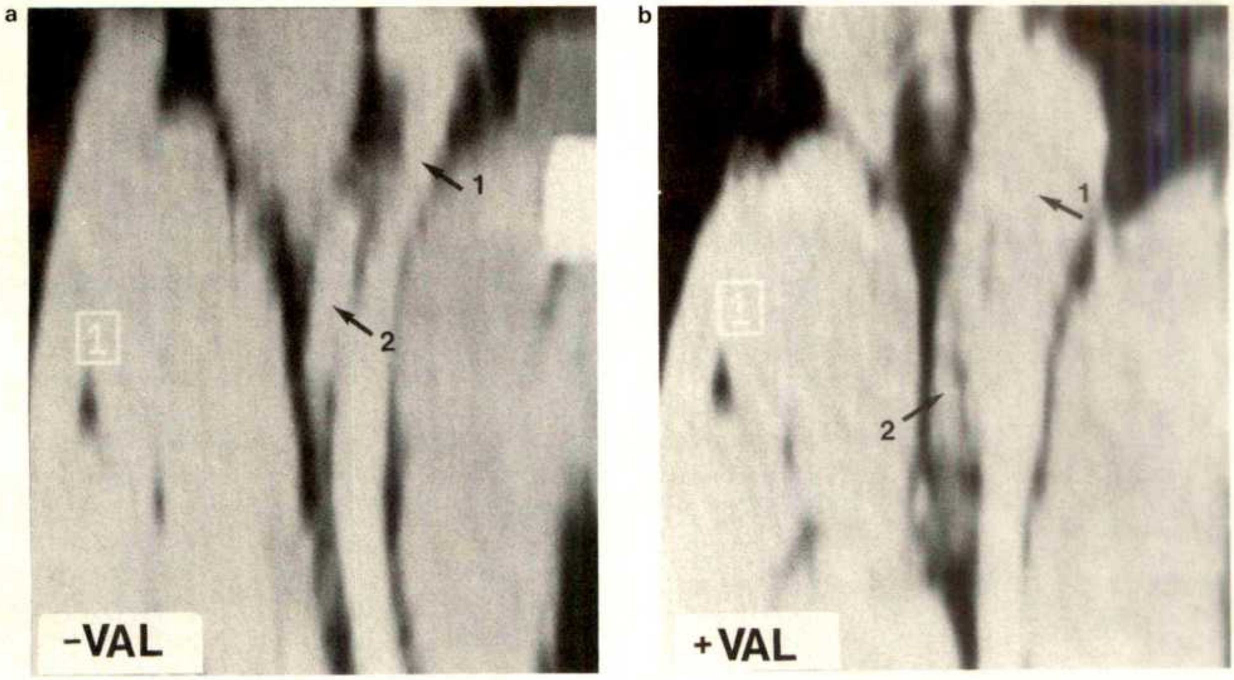

Figure 3 *Frontal sections.* **a** *Constructed longitudinal computed tomographic scan through the middle of the vein as it passes through the lacuna vasorum.* **b** *With increased intra-abdominal pressure, a longitudinal swelling is created comprising the distal part of the external iliac vein (1) and its transition to the femoral vein. The artery (2) keeps its diameter unchanged*

of the abdominal cavity, the conditions deep to the inguinal ligament are different. In this transitional zone the intraluminal pressure is conveyed down to the first competent valve in the femoral vein, while the pressure outside this sector of the vein is reduced to normal. The thin-walled vein will therefore bulge in this area.

Excessively increased abdominal pressure, enlargement of the femoral canal, and/or a functional decrease of the diameter of the vein are said to be predisposing factors for a femoral hernia[2,5–8]. To this we can add that an incompetent valve in the proximal part of the femoral vein will be another risk as it makes the bulging of the vein less likely.

It has been shown that the external iliac vein in 15–20 per cent of cases is equipped with a competent valve[4,9] (*Figure 4*). If that is combined with an absent or incompetent valve in the femoral vein, a reverse situation to the normal is created, i.e. a raised intra-abdominal pressure will squeeze the blood out of the vein in the femoral sheath and force the vein to collapse, thereby enlarging the inner ring of the femoral canal. Finally, it should be noted that this is compatible with the fact that competent valves are much more common in the right iliac vein and that right-sided hernias are twice as common as left-sided ones[4,10].

We have concluded that raised intra-abdominal pressure creates a local swelling of the vein in the femoral canal sufficient in size to close the canal and protect against herniation. The swelling which is produced by the intraluminal pressure is dependent on the existence of a competent valve in the proximal femoral vein.

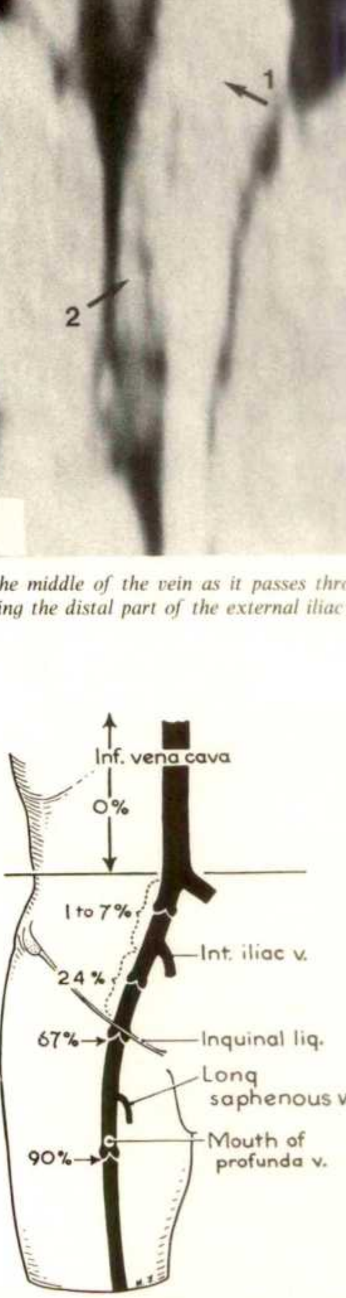

Figure 4 *Diagram showing the percentage incidence of valves in the iliac and femoral veins: Inf., inferior; Int., internal; lig., ligament; v., vein. (From Basmajian*[4]*, with permission of* Surgery, Gynecology and Obstetrics)

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Limb conservation for soft tissue sarcomas of the shoulder and pelvic girdles

Fifty-five patients with soft tissue sarcomas of the shoulder and pelvic girdles were treated between 1982 and 1987 with a consistent policy of limb conservation, using a wide variety of excisional and reconstructive surgical techniques and radical radiotherapy. Actuarial 5-year overall survival was 75 per cent for patients with low or intermediate grade tumours, and 38 per cent for those with high grade tumours (log rank test, $P<0{\cdot}05$*). Five-year local recurrence rates were 32 per cent for low or intermediate grade tumours, and 48 per cent for high grade tumours (log rank test, not significant). Multivariate analysis of the following risk factors for overall survival was performed: age, sex, tumour site, diameter, grade, inadequate surgical margins and local recurrence. Age over 55 years and high tumour grade emerged as independent prognostic variables for survival. Forequarter or hindquarter amputations were undertaken in seven of the 55 patients for local recurrence following previous limb-conserving surgery and radiotherapy. Local failure was not always salvaged by major amputation; satisfactory proximal tumour clearance was achieved in only two of seven patients undergoing major amputation; four of the seven patients developed stump recurrence, three of whom died with uncontrolled local disease. Meticulous attention to surgical and radiotherapeutic technique is required to minimize the incidence of local recurrence while maintaining satisfactory limb function.*

Keywords: Soft tissue sarcoma, limb conservation, forequarter amputation, hindquarter amputation

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Soft tissue sarcomas of the shoulder and pelvic girdles are a particularly difficult group of tumours to manage. They are frequently large and deeply situated at initial presentation, and are associated with a poorer prognosis than sarcomas situated more distally on the limbs[1]. Limb-sparing surgery is technically challenging: the tumours often lie in relation to major neurovascular bundles, and adequate proximal margins can be difficult to obtain when the tumour lies adjacent to the chest wall or pelvis. The factors that may make limb-sparing surgery with satisfactory tumour clearance impossible, such as extension of tumour above the inguinal ligament or across the midline, are the same factors that militate against performing a satisfactory amputation.

Since 1982 we have treated 55 cases of soft tissue sarcoma of the shoulder and pelvic girdles with a consistent policy of combined modality limb-conserving therapy, and have undertaken a prospective study of prognostic variables. In this article we review some of the technical aspects of limb-sparing surgery and amputation in the management of these tumours, and the factors associated with local or distant failure.

Patients and methods

Fifty-five patients with soft tissue sarcomas arising within the tissues of the shoulder or pelvic girdles have been referred to this unit for definitive management since 1982. Patients with primary bone neoplasms, childhood embryonal rhabdomyosarcoma, or tumours considered to have arisen within the thigh or arm have been excluded from this report.

Of the 55 patients, 43 were referred with previously untreated primary soft tissue sarcomas, usually following an incision biopsy or limited excisional surgery elsewhere. Twelve of the 55 patients were referred for management of locally recurrent disease following initial definitive management at other institutions. The median age of the patients was 43 years (range 11–84 years), and there were 29 male and 26 female patients. The four patients with rhabdomyosarcoma were over 18 years of age. Our policy was to undertake limb-sparing surgery rather than amputation whenever possible, reserving amputation for otherwise untreatable local disease.

The margins of surgical clearance were recorded as radical, wide, marginal or intracapsular according to the criteria described by Enneking *et al.*[2]. Patients with high grade tumours, or with low or intermediate grade tumours in whom a marginal or intracapsular excision had been performed, received postoperative radical radiotherapy to the tumour bed and 'at risk' surrounding tissues (23 of 43 previously untreated patients). Seven of the previously untreated patients received palliative irradiation for inoperable tumours, and two received preoperative irradiation for bulky tumours. Eleven of the previously untreated patients did not receive radiotherapy for a variety of reasons (four low grade tumours, three radiation-induced tumours, two with concomitant metastases, one wound breakdown, one child). Of the 12 recurrent cases, six received radical adjuvant postoperative radiotherapy, five had received previous irradiation which precluded further radiotherapy and one had preoperative radiotherapy.

The patients have been followed up for a median of 3 years (range 1·5–7·0 years). Actuarial local recurrence-free survival and overall survival were calculated according to the method of Kaplan and Meier[3], and the log rank test of statistical significance was used to compare differences between stage subgroups[3]. The tumours were graded according to a three-point scale into 'high', 'intermediate' or 'low' grade by one pathologist (C.F.), but intermediate and low grade tumours have been considered together in this anlaysis because no significant survival difference was found between these two groups. The following factors were entered into a multivariate analysis of risk factors for overall survival for the 43 patients presenting with previously untreated disease: age, sex, tumour grade (high *versus* low/intermediate), site (shoulder *versus* pelvis), maximum tumour diameter, surgical margins (radical/wide *versus* marginal/intracapsular) and local recurrence. Adjuvant radiotherapy was not analysed as a separate factor as it had been given consistently to high risk cases. Similarly, the influence of adjuvant chemotherapy was impossible to determine because of the

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Table 1 *Site of limb girdle sarcomas*

Site	*n*
Shoulder	
Axilla	5
Periscapular	10
Periclavicular	1
Deltoid	3
Pelvis	
Buttock	17
Groin/femoral triangle	17
Intrapelvic (iliac fossa)	2
Total	55

Table 2 *Histology of limb girdle sarcomas*

Histology	*n*
Malignant fibrous histiocytoma	20
Synovial sarcoma	4
Liposarcoma	11
Sarcoma (not otherwise specified)	8
Epithelioid sarcoma	1
Embryonal sarcoma	1
Mesenchymal chondrosarcoma	1
Rhabdomyosarcoma	4
Fibrosarcoma	3
Haemangiosarcoma	1
Malignant peripheral nerve sheath tumour	1
Total	55

Table 3 *Surgery for previously untreated primary tumours*

Procedure	*n*
Excisional procedures	
Biopsy only	8
Re-excision of tumour bed	5
Soft part resection	26
Partial pelvic bony resection	2
Scapulectomy	2
Total	43
Reconstructive procedures	
Myocutaneous flaps	4
Rotation skin flap	1

heterogeneous nature of the regimens employed. The data were analysed by the Cox proportional hazards technique[4].

Results

The sites of the tumours are shown in *Table 1*, the most common sites being buttock, groin or femoral triangle, and periscapular tissues. Two intrapelvic tumours were included within the definition of 'pelvic girdle' because they were situated within the iliopsoas muscle and were potentially resectable by hindquarter amputation. *Table 2* lists the histological subtypes. There were 37 high grade, ten intermediate and eight low grade tumours. The mean tumour diameter was 10·5 cm (median 10 cm, range 1–30 cm).

The surgical procedures performed for the previously untreated cases are listed in *Table 3*. In eight cases the tumour was considered to be inoperable, and biopsy alone was performed. In five patients a re-excision of tumour bed was performed after limited excisional surgery elsewhere; three of these five patients had histological evidence of residual disease. Twenty-six patients had major soft tissue resections; compartmental resection was performed when possible, but was not feasible when the tumour had arisen within the axilla or femoral triangle, or had infiltrated outside the confines of its compartment of origin. The margins of excision are shown in *Table 4*. Radical or wide tumour resection was possible in only 15 of 35 (43 per cent) operable primary tumours. Two patients had a major nerve excised in continuity with the tumour (femoral and median) and one patient underwent excision of the external iliac vein without vascular reconstruction or significant postoperative morbidity.

Two patients had partial pelvic bony resections, in which a section of ilium was excised in continuity with the specimen to obtain wide tumour clearance without the need for hemipelvectomy; in both cases preoperative computed tomography had suggested invasion through the periosteum. Two patients had scapulectomy for bulky periscapular tumours, and wide clearance was achieved while preserving a functional upper limb.

Overall survival for the previously untreated tumours is shown in *Figure 1*. The probability of 5-year survival was 75 per cent for low/intermediate grade tumours and 38 per cent for high grade tumours (log rank test, $P < 0{\cdot}05$). The probability of local recurrence for the previously untreated tumours is shown in *Figure 2*. The probability of a local recurrence by 5 years was 32 per cent for low/intermediate grade tumours and 48 per cent for high grade tumours (log rank test, $\chi^2 = 0{\cdot}25$, not significant). Of the 43 patients with previously untreated primary soft tissue carcinomas, 14 had a local recurrence of whom eight had no evidence of metastatic disease at the time of local recurrence.

Table 4 *Margins of excision at primary definitive surgery*

Margin	*n*
Radical	2
Wide	13
Marginal	16
Intracapsular	4
Biopsy only	8
Total	43

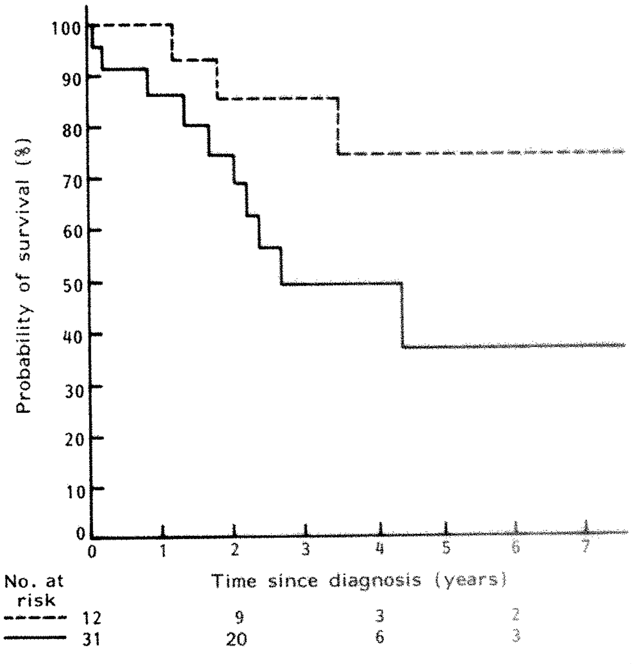

Figure 1 *Actuarial overall survival of 43 patients with previously untreated primary soft tissue sarcomas of the shoulder and pelvic girdles: ——, patients with high grade tumours; - - -, patients with low/intermediate grade tumours. The numbers of patients at risk at each time interval are shown.* (*Log rank test,* P<0·05)

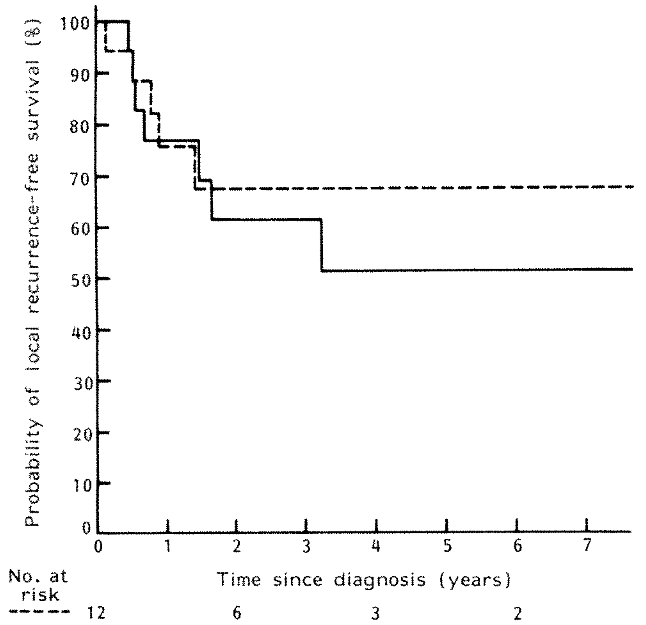

Figure 2 *Actuarial local recurrence-free survival of the group of patients detailed in* Figure 1: ——, *patients with high grade tumours;* - - - -, *patients with low/intermediate grade tumours. The numbers of patients at risk at each time interval are shown. (Log rank test, not significant)*

Table 5 *Multivariate analysis of risk factors for overall survival*

Factor	Relative risk	Reduction in log likelihood
High grade	15·3 (1·6–141·0)	$\chi^2 = 6{\cdot}8$ $P = 0{\cdot}009$
Age over 55 years	5·8 (1·3–26·5)	$\chi^2 = 4{\cdot}1$ $P = 0{\cdot}043$
Site (pelvis)	2·9 (0·6–13·8)	$\chi^2 = 2{\cdot}0$ $P = 0{\cdot}16$
Local recurrence	2·1 (0·5–12·1)	$\chi^2 = 1{\cdot}64$ $P = 0{\cdot}2$
Margins of clearance (inadequate)	1·7 (0·3–8·5)	$\chi^2 = 0{\cdot}62$ $P = 0{\cdot}4$

Values in parentheses are 95 per cent confidence intervals

The factors significantly associated with impaired overall survival on multivariate analysis were: high tumour grade ($P = 0{\cdot}009$) and age over 55 years ($P = 0{\cdot}043$; *Table 5*). Age did not emerge as an independent risk factor when tumour-specific mortality was analysed.

A total of 53 surgical procedures was performed for local recurrence in 26 patients (12 patients referred for management of local recurrence, plus 14 of 43 patients having local recurrence following primary treatment at this institution). The procedures performed are shown in *Table 6*. Of the 53 procedures, 23 were definitive limb-sparing resections for recurrent disease, including chest wall resection in two patients (both repaired with polypropylene mesh and a myocutaneous flap) and an abdominoinguinal excision of recurrent fibrosarcoma infiltrating from groin to external iliac vessels in one patient, using the Karakousis approach[5]. Three patients with recurrent groin disease required myocutaneous flap repair using tensor fasciae latae, rectus abdominis and a latissimus dorsi microvascular free flap, respectively.

Major amputation was performed in seven patients: two forequarters and five hindquarters. The amputations were all undertaken for uncontrolled local recurrence after previous limb-sparing surgery and radical radiotherapy. Amputation was performed in the presence of known distant metastases in two patients for palliation of ulcerating local disease. In five patients the margin of clearance obtained at amputation was considered to be 'marginal' or 'intracapsular', and in only two patients was it considered to be 'wide'; none was radical. Five of the seven amputees have died, at a median of 4 months (range 3–12 months) from the date of amputation. Three of these amputees died with further local recurrence within the amputation stump; in two of these patients no clinical evidence of distant metastatic disease was present, suggesting that they may have died from rather than with uncontrolled local disease. Of the two amputees who are alive, 12 and 30 months after amputation respectively, one has had a stump recurrence treated by marginal surgical excision and both have metastases. A total of four amputees have thus suffered a stump recurrence.

Discussion

Limb-sparing surgery combined with radical preoperative or postoperative radiotherapy has become the standard treatment for soft tissue sarcomas of the limbs and limb girdles in recent years. The results of this approach in terms of local control and survival have been shown to be equivalent to those obtained by radical surgery alone in several major retrospective series[6–10]. A prospective randomized trial of limb-sparing surgery from the National Cancer Institute in the USA demonstrated an increased risk of local recurrence in high grade sarcomas of the extremities treated by such surgery compared with amputation, but no impairment of overall survival was seen[11]. Several centres add chemotherapy to the combined modality treatment of these tumours (for example, with preoperative intra-arterial Adriamycin®, Farmitalia Carlo Erba Ltd., St. Albans, UK[12], or with postoperative adjuvant combination chemotherapy regimens[7]), but the degree of survival advantage or improved local control conferred by chemotherapy is still unclear[13].

The risk factors associated with poor overall survival (grade and age) in our multivariate analysis are in accordance with those reported by other authors for soft tissue sarcomas of the limbs[6,9,11,14–18]. Tumour size and inadequate surgical margins, which have correlated with survival in other series, did not influence survival in our own analysis, and local recurrence did not emerge as an independent risk factor. This may be a reflection of the value of adjuvant irradiation in the treatment of primary and recurrent disease.

Limb-sparing combined modality therapy is particularly difficult in the management of tumours in the shoulder and pelvic girdles. In only two of the 43 cases reported here was radical excision of a primary tumour possible; in both cases the tumours had arisen within the gluteus maximus muscle and a compartmentectomy could be performed. Wide excision of bulky high grade tumours still proved possible without amputation by using the techniques of scapulectomy in two patients and partial pelvic resection in two patients. However, in the majority of primary tumours (20 of 43) the excision was marginal or intracapsular, and eight out of 43 patients had tumours that were considered to be inoperable on the basis of preoperative clinical examination and computed tomography.

Table 6 *Surgery for local recurrence*

Procedure	*n*
Intracapsular resection (debulking)	21
Soft part resection	20
Chest wall resection	2
Abdominal hysterectomy and oöphorectomy	1
Small bowel resection	1
Karakousis operation	1
Forequarter amputation	2
Hindquarter amputation	5

For locally recurrent sarcomas, the situation was even more difficult. The tumour boundaries tended to be indistinct, and infiltration into adjacent muscle compartments, bone, joints or other tissues often made further limb–sparing surgical excision impossible. However, in contrast to more distally situated limb sarcomas, in which control of local failure can usually be achieved by amputation through non-involved tissue at or above the proximal joint, local control by amputation was not always possible. Extension of tumour across the midline, into the pelvis, or into the iliopsoas muscle made hindquarter amputation impossible for two patients with local recurrence, and only palliative for another. Similarly, the finding of recurrent tumour around the brachial plexus at forequarter amputation rendered this a palliative procedure for one patient.

Surgical options less mutilating than forequarter or hindquarter amputation, such as the Tikhoff–Lindberg procedure[19] (in which the scapula, clavicle and head of humerus are excised leaving the distal limb with its neurovasculature intact) or internal hemipelvectomy (in which the hemipelvis is removed but the lower limb with its neurovascular connections is preserved), may be appropriate for some primary bone tumours or for some soft tissue tumours of the proximal limb or limb girdle[20–23]. None of the recurrent limb girdle soft tissue sarcomas in this series was suitable for such surgical options, as the tumours had infiltrated too widely around neurovascular bundles and limb girdle musculature.

Modified hindquarter amputation was performed in one patient in this series, in whom the iliac bone was sectioned horizontally at the level of the sciatic notch thus preserving the sacroiliac joint and posterior ilium[21]. This involves an easier dissection and leaves a better 'shelf' for supporting a prosthesis, but is possible only in carefully selected patients. One of the four patients having a classical hindquarter amputation required an anterior skin flap based on the external iliac vessels, as the tumour and previous surgical scar had compromised the buttock skin[24,25].

The high incidence of stump recurrence following forequarter or hindquarter amputation reflects the difficulty of achieving satisfactory proximal tumour clearance. Adjuvant perioperative radiotherapy to the stump has been advocated[18], but was not possible in this series because of the proximal extent of the original radiotherapy fields.

Soft tissue sarcomas of the shoulder and pelvic girdles require meticulous attention to surgical and radiotherapeutic technique to minimize the incidence of local recurrence while maintaining satisfactory limb function. Expertise in a wide variety of excisional and reconstructive procedures is essential. Local failure may not be salvageable by subsequent amputation.

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Arteriogram scoring systems and Pulse Generated Run-off in the assessment of patients with critical ischaemia for femorodistal bypass

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Conventional arteriography is the investigation of choice in patients with critical ischaemia to select the site for the distal anastomosis of a femorodistal bypass. Several arteriographic scoring systems have been devised in an attempt to quantify the run-off. More recently Pulse Generated Run-off and intraoperative peripheral resistance measurements have been proposed as better predictors of early graft patency. Eighty-eight consecutive femorodistal bypass grafts were studied using Pulse Generated Run-off (PGR), conventional and intra-arterial digital subtraction arteriography (DSA) and peripheral resistance measurement. Three widely used arteriographic scoring systems were used to grade the arteriographic run-off. There were significant correlations between the scoring systems and the measured peripheral resistance, although PGR correlated better with peripheral resistance than arteriography ($r_S = -0{\cdot}59$, $P < 0{\cdot}001$). Intra-arterial DSA improved the correlation between the arteriogram scoring systems and the measured peripheral resistance in the distal popliteal artery, but not in single calf vessels. In contrast, PGR correlated much better with peripheral resistance in single calf vessels ($r_s = -0{\cdot}82$, $P < 0{\cdot}001$). We recommend that selection for femorodistal reconstruction be based on a combination of intra-arterial DSA and PGR. PGR will identify patent distal calf vessels not seen on arteriography and determine their continuity with the pedal arch, two features which are essential prerequisites for successful femorodistal bypass.

Keywords: Femorodistal bypass, conventional arteriography, digital subtraction arteriography, critical ischaemia, pulse generated run-off

Since Brooks performed the first femoral arteriogram in September 1923[1], conventional preoperative arteriography has become the investigation of choice in the assessment for vascular reconstruction of patients with critical ischaemia. The development of computerized digital subtraction techniques has improved the visualization of the distal vasculature[2], especially when combined with reactive hyperaemia[3]. Arteriography helps identify patients who may benefit from an improved inflow, either by a proximal reconstruction or by balloon dilatation and it provides the surgeon with information to help select the appropriate vessel and level of the distal anastomosis.

Grafts performed to calf vessels in continuity with the pedal arch have significantly better short- and long-term patency rates than those without such continuity[4-6]. In critical ischaemia, identification of the distal run-off may be hampered by a combination of factors including severe multisegment disease, poor myocardial function and ectatic vessels, all of which lead to rapid layering and sedimentation of contrast media. As a result, the arteriogram may be misleading and may fail to identify patent distal vessels in the lower calf[7]. The identification of patent calf vessels has been improved by Pulse Generated Run-off (PGR)[7], a non-invasive test which gives a semi-quantitative analysis of each of the calf vessels and its relative contribution to the pedal arch.

In an attempt to improve the predictive value of arteriography, various scoring systems have been devised ranging from the simple to the complex[8-11]. More recently, peripheral resistance has been shown to be an excellent predictor of early graft function[12-14] and in this study the PGR and arteriogram scores were correlated with the measured peripheral resistance. The impact of intra-arterial digital subtraction arteriography (DSA) on the prediction of peripheral resistance was also assessed.

Patients and method

Eighty-eight consecutive femorodistal non-reversed vein grafts were performed in 57 men and 31 women of median age 71 years (range 41–87 years). All grafts were performed for critical ischaemia[15]: 37 for rest pain and 51 for tissue necrosis. Twenty-eight grafts were anastomosed to a single calf vessel, nine to the tibioperoneal trunk and the remaining 51 to the distal popliteal artery. Before surgery all patients underwent non-invasive assessment which included Doppler ankle pressures and a PGR study.

Pulse Generated Run-off

The patients were fully rested for 10 min before starting the study. The examination was performed in the supine position with the heels resting on a support. An inflatable cuff was wrapped tightly around the upper calf and rapidly inflated and deflated over a pressure of 300 mmHg at 50 cycles per minute. An assessment of all three calf vessels and the pedal arch was made at the ankle using a 10 MHz hand-held Doppler velocimeter[7] (*Figure 1*). The resultant Doppler waveforms were scored as follows: 2 points for a biphasic wave, 1 point for a monophasic wave and no point for an absent signal (*Figure 1*). Thus a possible maximum score of 6 could be obtained for each leg, and 6 represents an excellent run-off.

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Arteriography

A routine preoperative conventional arteriogram was performed in all cases. In the latter half of the series (48 cases) conventional arteriography was supplemented by intra-arterial DSA. The calf vessel run-off was reported independently of the PGR score, peripheral resistance and graft outcome. Three arteriographic scoring systems were used.

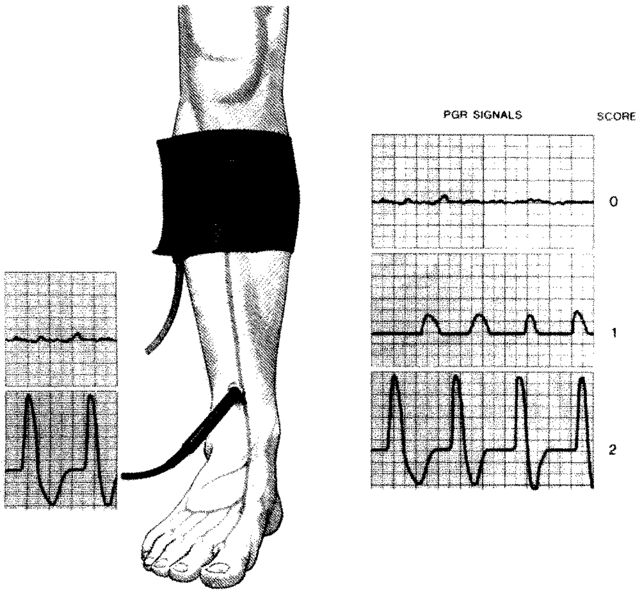

Figure 1 *Pulse Generated Run-off and scoring system. This shows the cuff around the upper calf with a 10 MHz Doppler pencil probe insonating the anterior tibial artery. The top trace shows a non-pulsatile signal and below the same signal augmented by the Pulse Generated Run-off*

Scoring system A. Two points were given to a widely patent vessel to the ankle, 1 point for a diseased but patent vessel to the ankle and no points for an occluded vessel, thus giving a range from 0 to 6, where 6 represents an excellent run-off (*Figure 2a*).

Scoring system B. In this scoring system the calf vessels were assessed over the first 5 cm from their origin. For a normal vessel 2 points were given, 1 point for a diseased vessel with a greater than 50 per cent stenosis and no points for an occlusion[8], giving a possible range of 0 to 6 (*Figure 2b*).

Scoring system C. In an attempt to standardize the various arteriographic scoring systems the Committee on reporting standards of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery (SVS and ISCVS) devised a new run-off grading system which could be applied to any level of the infrainguinal arterial tree. The run-off was assessed at the proposed site of the distal anastomosis. This is a complex scoring system and is well described elsewhere[11]. Essentially the graded scoring system is based upon the patency of the vessel and the relative contribution to the outflow tract. A score of 1 corresponded to an excellent run-off and 10 to a blind segment (*Figure 2c* and *d*).

Operative measurement of peripheral resistance

Peripheral resistance was measured by introducing a newly produced soft 6/8 Fr (Portex®, Portex Ltd, Hythe, UK) tapered end catheter into the vessel chosen for the distal anastomosis (*Figure 3*). A hand infusion of heparinized blood was performed at a physiological pressure of about 80–100 mmHg. Pressure (P) was measured by a pressure transducer and flow (Q) by a recently developed ultrasonic flowmeter[16].

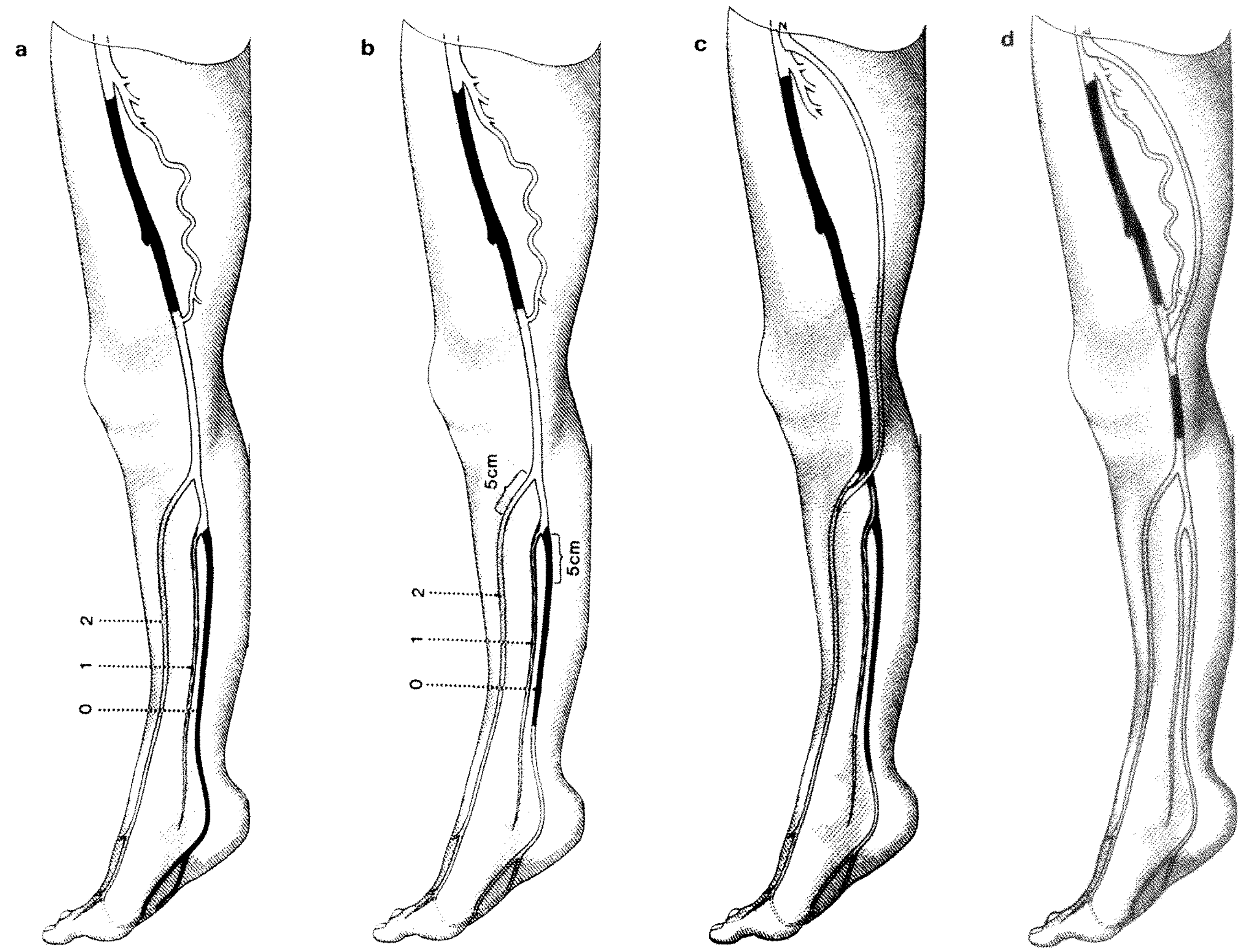

Figure 2 **a** *Arteriogram scoring system A*; **b** *arteriogram scoring system B*; **c** *arteriogram scoring system C (showing a graft anastomosed to a patent anterior tibial artery), score = 1; and* **d** *arteriogram scoring system C (showing a graft anastomosed to a popliteal blind segment), score = 10 poor run-off*

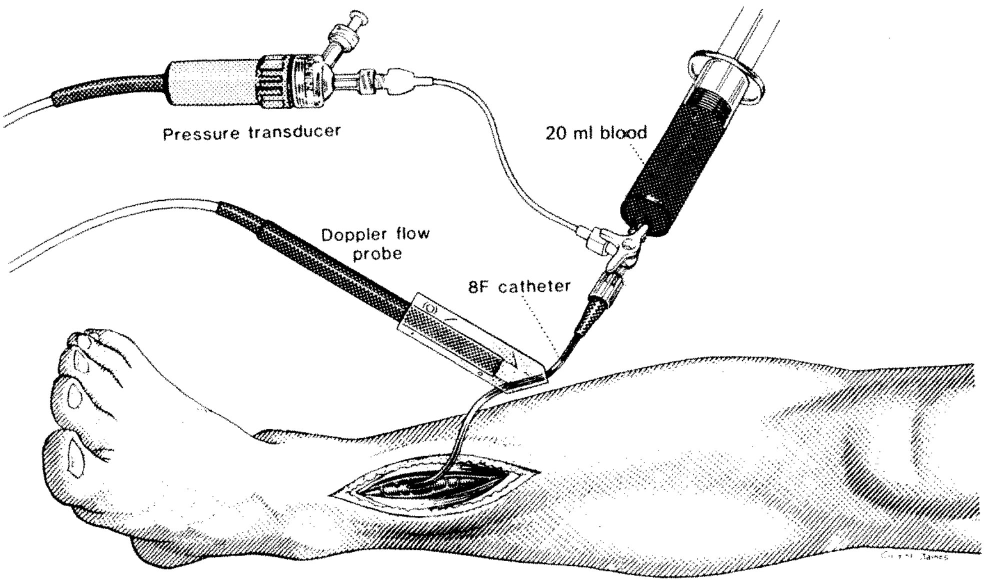

Figure 3 *Method of peripheral resistance measurement. This shows a soft 8 Fr catheter inserted into the distal anterior tibial artery. During the infusion of heparinized blood, pressure is measured by the pressure transducer and flow by the Doppler flow probe linked to the flowmeter*

Table 1 *Spearman rank correlations between peripheral resistance and either Pulse Generated Run-off or arteriogram scoring systems*

Correlation	Pulse Generated Run-off	Score A	Score B	Score C
PR r_S	−0·59*	−0·36*	−0·33*	0·33*

PR, peripheral resistance; * $P<0.001$

Simultaneous recordings of pressure and flow were converted by an Apple 2E (Apple Computer Company, Cupertino, California, USA) microcomputer into peripheral resistance units (PRUs), where:

$$1\ \text{PRU} = 1\ \text{mmHg}/1\ \text{ml blood flow per min}$$

The peripheral resistance was then calculated by subtracting the resistance of the catheter R_C from the total resistance R_T. The catheter resistance R_C was calculated by measuring the pressure and flow during an infusion of heparinized blood through an open ended catheter:

$$\text{Peripheral resistance (PR)} = R_T - R_C$$

Results

Correlation between peripheral resistance and either Pulse Generated Run-off or arteriogram scoring systems

Eighty-eight femorodistal bypass grafts were analysed to determine the value of PGR and the arteriographic scoring systems A, B and C and these values were correlated with the measured peripheral resistance at the time of femorodistal bypass.

There was a significant correlation between the arteriogram scoring systems A, B and C and the measured peripheral resistance (*Table 1*). However PGR correlated much better with peripheral resistance ($r_S = -0.59$, $P<0.001$) than any of the arteriogram scoring systems A, B or C (*Figure 4*).

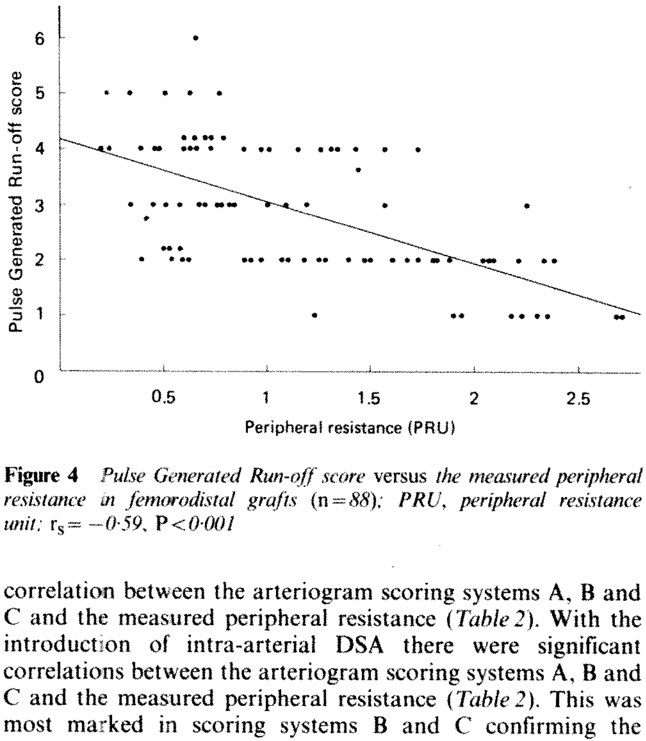

Figure 4 *Pulse Generated Run-off score* versus *the measured peripheral resistance in femorodistal grafts* (n=*88*)*; PRU, peripheral resistance unit;* $r_S = -0.59$, $P<0.001$

Influence of intra-arterial digital subtraction arteriography on the scoring systems

During this consecutive series, intra-arterial DSA became available and was routinely used in the assessment of patients with critical ischaemia. Two groups were subsequently identified and analysed to assess the impact of intra-arterial DSA: group I, conventional arteriography only, 40 patients; and group II intra-arterial DSA, 48 patients.

In the conventional arteriogram group there was a poor correlation between the arteriogram scoring systems A, B and C and the measured peripheral resistance (*Table 2*). With the introduction of intra-arterial DSA there were significant correlations between the arteriogram scoring systems A, B and C and the measured peripheral resistance (*Table 2*). This was most marked in scoring systems B and C confirming the improved visualization of calf vessels using the intra-arterial DSA technique.

In both groups I and II there was a significant correlation between the PGR score and the measured peripheral resistance ($r_S = -0.74$, $P<0.001$ and $r_S = -0.44$, $P<0.001$ respectively). The variability between groups I and II is almost certainly related to the inability of PGR to detect proximal calf vessel disease.

The role of PGR and intra-arterial DSA in determining the site of distal anastomosis

Groups I and II were analysed to assess the role of both PGR and intra-arterial DSA in determining the suitability of patients for either proximal (distal popliteal) or distal calf (single calf vessels) reconstructions.

Proximal calf (distal popliteal) reconstructions. The arteriogram scores A, B and C derived from the intra-arterial DSA

Table 2 *Spearman rank correlations between peripheral resistance and arteriogram scoring systems for groups I and II*

Group	*n*	Correlation	Pulse Generated Run-off	Score		
				A	B	C
I (conventional arteriography)	40	PR r_S	−0·74†	−0·34*	−0·07‡	0·13‡
II (intra-arterial DSA)	48	PR r_S	−0·44†	−0·46†	−0·56†	0·55†

DSA, digital subtraction angiography; PR, peripheral resistance; *$P<0{\cdot}05$; †$P<0{\cdot}001$; ‡not significant

Table 3 *Correlation of peripheral resistance with arteriographic scoring systems in reconstructions to the distal popliteal artery*

Group	*n*	Correlation	Score		
			A	B	C
I (conventional arteriography)	22	PR r_S	−0·25‡	−0·10‡	0·24‡
II (intra-arterial DSA)	29	PR r_S	−0·43*	−0·56†	0·55†

DSA, digital subtraction angiography; PR, peripheral resistance; *$P<0{\cdot}01$; †$P<0{\cdot}001$; ‡not significant

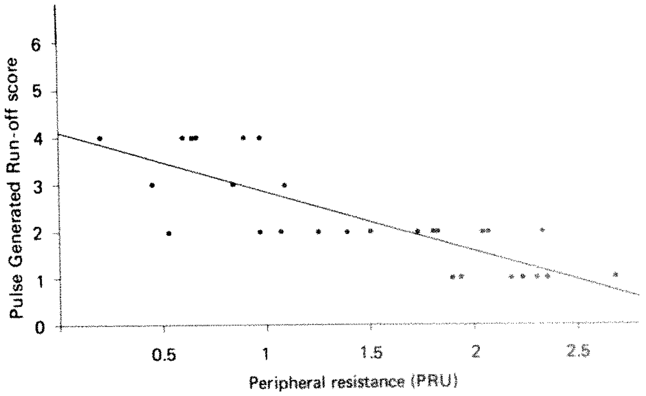

Figure 5 *Pulse Generated Run-off score* versus *the measured peripheral resistance in single calf vessel grafts* (n = *28*)*; PRU, peripheral resistance unit;* $r_S = -0{\cdot}82$*;* $P<0{\cdot}001$

views correlated better with the measured peripheral resistance than the scores from the conventional arteriograms (*Table 3*). In particular, scoring systems B and C correlated well with the measured peripheral resistance. In the 51 distal popliteal grafts there was reasonable correlation between the PGR and peripheral resistance ($r_S = -0{\cdot}36$, $P<0{\cdot}01$).

Distal calf (single calf vessel) reconstructions. Neither conventional nor intra-arterial DSA derived arteriogram scores A, B and C correlated with the measured peripheral resistance (*Table 4*). This probably reflects the limitation of arteriography particularly in patients with severe multisegment disease. There was excellent correlation between PGR and the measured peripheral resistance ((*Figure 5*) in the single calf vessel group ($r_S = -0{\cdot}82$, $P<0{\cdot}001$)

Discussion

Conventional arteriography has been the definitive investigation in patients with critical ischaemia and the decision to perform surgery is based on the visualization of an adequate run-off[17–19]. In patients with a single calf vessel, continuity with the pedal arch is a decisive factor in short- and long-term patency[5–7]. In the presence of multisegment disease and poor myocardial function visualization of calf vessel run-off and pedal arches using arteriography may prove impossible. The introduction of intra-arterial DSA has resulted in better vessel resolution with a lower contrast load but may not show very distal patent calf vessels.

Peripheral resistance has recently been shown to be of predictive value in the peroperative assessment of patients for femorodistal bypass but is an intraoperative technique and does not allow preoperative selection of patients[12–14].

In an attempt to improve the predictive value of arteriography various scoring systems have been devised, the simplest being graded 0–3, 1 point being given for each patent calf vessel[8–11]. LaMorte *et al.* found this simple scoring system to be of little predictive value in terms of the peripheral resistance measured at the time of surgery[10]. The poor correlation between the arteriogram score and the peripheral resistance was attributed to: (1) an inability of the scoring system to differentiate between good and bad vessels, and (2) an assumption that all three calf vessels contributed equally to the overall peripheral resistance. On the basis of these criticisms LaMorte devised a new scoring system which took into account the arch in the overall determination of peripheral resistance. This produced a better correlation with peripheral resistance, $r=0{\cdot}61$. One of the criticisms against the addition of an arch score is that some centres may not have the equipment, technical expertise or time to visualize these vessels.

In an attempt to standardize the use of arteriographic scoring systems in reporting run-off, the adhoc Committee (SVS and ISCVS) on reporting standards devised a novel method of assessing run-off[11]. The run-off was graded at the site of the proposed distal anastomosis. The grading system took into account the vessel chosen for the anastomosis, the severity of disease, patency of the arch if applicable and a base resistance. Peterkin *et al.* reported that the SVS/ISCVS scoring system correlated with the measured peripheral resistance ($r=0{\cdot}30$, $P<0{\cdot}01$), but was improved by weighting the individual calf vessel by means of multiple linear regression[20].

In this study three separate arteriogram scoring systems were correlated against the peripheral resistance. In the analysis of all 88 grafts there was poor correlation between the arteriogram scoring systems A, B and C and the peripheral resistance. In contrast, PGR correlated significantly with the measured peripheral resistance ($r_S = -0{\cdot}59$, $P<0{\cdot}001$).

The introduction of intra-arterial DSA produced an overall improvement in the correlation between the arteriogram scores and the peripheral resistance. In particular it improved the visualization of the proximal calf vessels and the subsequent correlation between the arteriogram scores and peripheral resistance. The better correlations with systems B and C probably reflect the superior methods of scoring. In system B the assessment was based over the first 5 cm of the calf vessel and in scoring system C the grading was based at the level of the distal anastomosis. Although system C is theoretically more attractive by basing the run-off at the level of the distal anastomosis, system B is much easier to apply and produces a similar correlation with peripheral resistance.

PGR correlates moderately well with peripheral resistance with an overall correlation for the 51 distal popliteal grafts of $r = -0{\cdot}36$. PGR in the present form does not assess the proximal calf vessels very well and this accounts for the poor correlation in the proximal grafts.

Table 4 *Spearman rank correlations between peripheral resistance, Pulse Generated Run-off and arteriographic scoring systems in reconstructions to single calf vessels*

Group	Correlation	Pulse Generated Run-off	Score		
			A	B	C
I (conventional angiography)	PR r_S	−0·80*	−0·2†	0·44†	−0·49†
II (intra-arterial DSA)	PR r_S	−0·86*	−0·39†	−0·38†	0·43†

DSA, digital subtraction angiography; PR, peripheral resistance; PGR, Pulse Generated Run-off; * $P < 0{\cdot}001$; † not significant

In the distal calf reconstructions the arteriogram scores derived from both the conventional and intra-arterial DSA films failed to correlate with the measured peripheral resistance. These results highlight some of the limitations of arteriography and the methods of scoring in patients with patent distal calf vessels not in continuity with the popliteal artery. By contrast PGR correlated extremely well with peripheral resistance in the single calf vessel group ($r_s = -0{\cdot}82$, $P < 0{\cdot}001$). This suggests that PGR is a superior test of calf vessel patency and should be used to select patients for distal reconstruction.

The use of intra-arterial DSA in combination with conventional arteriography has improved the visualization of calf vessels particularly in the proximal calf. The aggressive approach to the demonstration of these vessels must be balanced against problems related to increasing contrast dose. In most patients this is not a problem when using DSA but is when using conventional arteriography.

Arteriography gives anatomical information with limited functional data. PGR on the other hand provides the surgeon with a semiquantitative assessment of calf vessel run-off. It can also be used to map out the pedal arches and determine which calf vessels are in continuity with the arch. This is extremely helpful when planning surgery.

We conclude that selection of patients for proximal calf vessel reconstruction can be based on arteriogram scoring systems derived from intra-arterial DSA; PGR may help this level by showing continuity of calf vessels with the pedal arch.

Distal reconstruction should not be denied to patients who have no evidence of run-off on either conventional arteriography or intra-arterial DSA. PGR may identify patent distal calf vessels and determine their continuity with the pedal arches, both of which are essential prerequisites in successful femorodistal reconstruction. We feel that PGR is the method of choice for selecting the appropriate vessel for distal calf reconstruction.

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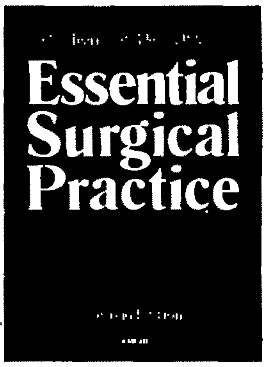

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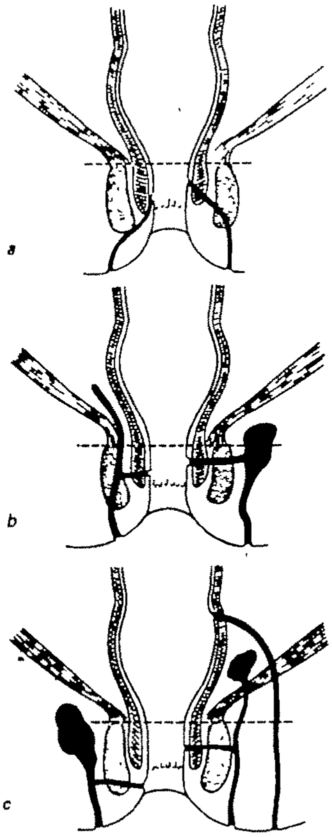

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Management of hyperparathyroidism in pregnancy

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It has been suggested that all women diagnosed as hyperparathyroid during pregnancy should undergo neck exploration while pregnant to avoid the fetal and maternal hazards of hypercalcaemia[1,2]. Conservative management of women with mild hyperparathyroidism, reserving surgery during pregnancy for more severe cases, has been suggested as an alternative[3,4]. We report on 15 women in whom hyperparathyroidism was associated with pregnancy.

Patients and methods

Our cases were identified from a series of 1550 patients treated surgically for hyperparathyroidism.

In ten (Patients 1–10, *Table 1*) the diagnosis was made postpartum after the development of neonatal tetany. In one (No. 11) parathyroidectomy had been performed 3 years before her re-presentation with recurrent hypercalcaemia (serum calcium 3·5 mmol/l) in a pregnancy which resulted in a stillbirth and a postnatal pulmonary embolus. Subsequent neck and mediastinal re-exploration revealed parathyroid carcinoma.

Four patients were diagnosed during pregnancy and two of these underwent surgery during pregnancy. Of the two managed conservatively, one (No. 12) presented at 26 weeks with a pathological jaw fracture and underwent an otherwise unremarkable pregnancy. Thereafter a parathyroid adenoma was removed from her neck. Recurrent hypercalcaemia resolved after two further neck explorations. She re-presented pregnant and hypercalcaemic again. After an uneventful full-term delivery, parathyroid carcinoma was confirmed after a fourth exploration. The second patient (No. 13) presented with hypertension in the first trimester, hypercalcaemia being diagnosed midpregnancy. Following a Caesarean delivery for breech presentation the neonatal course was normal. A parathyroid adenoma was subsequently excised.

Both women explored during pregnancy presented with hyperemesis gravidarum. One patient (No. 14) presented at 6 weeks with a serum calcium of 3·4 mmol/l and a previous history of hyperemesis in pregnancy. Neck exploration in the first trimester of the second pregnancy revealed only four suppressed parathyroid glands, confirmed by histology. She was transferred with persistent hypercalcaemia and renal calculi were also diagnosed. The patient's symptoms settled and it was elected to defer further investigation and surgery until after delivery. The remainder of the pregnancy was unremarkable and the neonatal course normal. Subsequently a parathyroid adenoma was removed from the anterior mediastinum and percutaneous nephrolithotomy performed.

The last patient (No. 15) had severe hyperemesis, became dehydrated, developed renal failure, pneumonia and severe hypertension and became drowsy. She was then found to be severely hypercalcaemic (serum calcium 4·5 mmol/l) with elevated serum parathormone. At neck exploration four gland hyperplasia was discovered. Normocalcaemia was restored and the remainder of the pregnancy was unremarkable.

Discussion

In this series the commonest presentation was symptomatic neonatal hypocalcaemia. There were no maternal deaths but one stillbirth associated with severe hypercalcaemia and parathyroid carcinoma in a woman who had had a previous parathyroid exploration occurred. No asymptomatic patients were diagnosed during pregnancy by chance.

Since the introduction of multichannel biochemical autoanalysers up to 60 per cent of cases of hyperparathyroidism in general are diagnosed as a chance finding[5]. Surgical exploration is none the less recommended for these patients[6,7]. The

Table 1 *Clinical details of 15 women with hyperparathyroidism associated with pregnancy*

Patient No.	Presentation	Surgery during or after pregnancy	Number of explorations	Pathology	Outcome/ comment
1	Neonatal tetany	After	1	Normal glands only: 4	Normocalcaemia ensued
2	Neonatal tetany	After	3(m2)	Adenoma	Good
3	Neonatal tetany	After	1	Adenoma	Good
4	Neonatal tetany	After	1	Adenoma	Good
5	Neonatal tetany	After	1	Adenoma	Good
6	Neonatal tetany	After	1	Adenoma	Good
7	Neonatal tetany	Before and after	2	Adenoma	Good/failed exploration elsewhere between pregnancies
8	Neonatal tetany	After	1	Adenoma	Good
9	Neonatal tetany	After	1	Adenoma	Good
10	Neonatal tetany	After	2(m1)	Adenomas: 2	Baby well, mother persistent hypercalcaemia
11	Bone cyst	Before and after 1st and before 2nd	3(m1)	Carcinoma	Stillbirth and pulmonary embolism, unrelated death 11 years later
12	Pathological jaw fracture in pregnancy 26/52	After 1st and before 2nd	4	Carcinoma	Babies well, lost to follow-up with bony metastases
13	Hypertension	After	1	Adenoma	Good
14	Hyperemesis gravidarum	During and after	2	Adenoma	Good/failed exploration elsewhere during pregnancy
15	Hyperemesis gravidarum	During	1	Hyperplastic glands: 4	Good

m number of mediastinal explorations; good outcome: mother normocalcaemic, baby otherwise well

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incidence of hyperparathyroidism in women of childbearing age suggests that the concurrence of this disease with pregnancy is more frequent than is indicated by the cases reported in the literature. The reasons for this discrepancy are that many asymptomatic cases remain undiagnosed as antenatal serum calcium estimation is not routinely performed and that uncomplicated cases are not reported. The suggestion that all pregnant woman with hyperparathyroidism should undergo surgery during pregnancy[1,2] is based, however, on earlier reports of conservatively managed cases noteworthy for complicated clinical courses. Thus Ludwig[8] reviewed 20 cases dating to the 1920s. Although he found a high incidence of obstetric complications many had florid hyperparathyroidism with serious complications. Furthermore, a relationship between these obstetric complications and hyperparathyroidism was not always obvious. Delmonico *et al.*[1] reviewed 14 further women managed conservatively and also noted a high incidence of neonatal tetany but only one neonatal death in a premature low birth weight baby whose mother had renal and bone complications.

During pregnancy there is transplacental passage of calcium ions but not parathormone from mother to fetus[9]. In hypercalcaemic mothers this is considered to lead to suppression of fetal parathyroid activity and such babies may develop tetany a few days after delivery. Transient neonatal tetany should not, however, be associated with long-term sequelae. Its occurrence in previous cases, usually the first sign of hyperparathyroidism in an otherwise unremarkable pregnancy, is not in itself a reason to advise neck exploration during pregnancy for all of these patients. In hyperparathyroid mothers neonatal hypocalcaemia is predictable and appropriate monitoring can be instituted.

In patients with severe or symptomatic hypercalcaemia, parathyroid exploration should be advised during pregnancy, the second trimester being suggested as the safest time[2]. In mild or asymptomatic cases it has been suggested that surgery can be safely deferred until after the pregnancy[3,4,10] and we agree with this policy.

The management of women with hyperparathyroidism during pregnancy requires a multidisciplinary approach preferably in a specialist centre[11]. If neck exploration is contemplated during pregnancy this clearly should be performed by an experienced parathyroid surgeon.

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Influence of suture technique on surgical glove perforation

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The prominence of diseases such as AIDS and hepatitis B has led to renewed interest in defining safe surgical techniques. Intact surgical gloves appear to be a barrier against human immunodeficiency virus[1,2] and recent studies suggest that glove perforation usually occurs during suturing, particularly laparotomy closure[3,4]. This trial investigates the contribution of active handling of the needle to glove perforation.

Patients and methods

From October 1987 to April 1988, 60 consecutive patients undergoing midline laparotomy were randomized to one of two methods of wound closure by random number allocation. All operations were performed by a single surgeon (P.C.). No patient was excluded

One closure method (A) restricted handling of the needle to the right hand by using a hand needle technique. The needle (Ethicon W711, 788, Ethicon Ltd, Edinburgh, UK) was both inserted and removed by the right hand. The left hand stabilized the wound but did not handle the needle.

The other closure method (B) restricted handling of the needle to the left hand by using an instrument technique. The right hand held a needle holder throughout, and was not exposed to sharp injury The left hand actively handled the needle (Ethicon W741, W786), removing it from the wound and remounting it

Gloves were changed before closing the wound and the new gloves were tested for pre-existing perforation. Wounds were then closed with a mass running suture of the abdominal wall layer, and interrupted simple sutures to skin. During wound closure, any overt glove puncture was noted and on completion of the operation the gloves were tested again and all perforations recorded. The gloves were then removed and the hands examined for evidence of injury.

Glove perforation was detected by an underwater immersion method The gloved hands were washed in sterile water for 60 s. Glove perforation allows water to be drawn in by capillary and osmotic action, passing through the starch powder within the glove This appearance is easily detectable by the naked eye.

Statistical analysis between the two methods of closure was made by non-parametric analysis (Mann–Whitney *U* test), or by the χ^2 test with Yates' correction as appropriate.

Results

There was no significant difference between the two groups in factors considered likely to influence the difficulty of wound closure (*Table 1*). Two gloves were found to be damaged when tested before wound closure.

There was no difference in the total number of perforations between the two methods, but all perforations occurred predominantly in the glove that actively handled the needle; the right glove in method A and the left glove in method B

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Table 1 *Comparison between the operations using the two closure methods*

	Method A ($n=32$)	Method B ($n=28$)
Emergency operations*	13 (41)	9 (32)
Muscle relaxation incomplete*	6 (19)	4 (14)
Operations lasting <1 h*	7 (22)	7 (25)
Wound length (cm)†	24 (13–41)	25·5 (10–41)
Wound depth (cm)†	4·5 (1–9)	4·5 (1–11)
Skin sutures per wound†	22 (11–37)	18 (8–42)

* Number of cases and percentage of group; † median and range. No differences were statistically significant

($P<0{\cdot}005$, χ^2 test). Unrecognized perforations also occurred more often in the glove that actively handled the needle ($P<0{\cdot}005$, χ^2 test), and more perforations were unrecognized during method A, in which a hand needle was used ($P<0{\cdot}005$, χ^2 test), though this method was quicker ($P<0{\cdot}05$, Mann–Whitney U test; *Table 2*).

Discussion

Several methods of detecting glove perforations have previously been described The measurement of electrical permeability[5,6] may, in practice, be oversensitive, as it detects perforations too small to admit radiolabelled albumin, or even a methylene blue molecule[7]. Filling the discarded glove with water then examining for leakage[4,8] cannot exclude pre-existing defects. The immersion method used in this trial was first used in 1939 by Devenish and Miles[9] and is particularly suitable for detecting pre-existing perforation.

In this study, perforation occurred with a frequency comparable to those previously reported in the literature[2,3,5–9]. There were only two occasions in which skin injury occurred; 60 operations were performed. Although method A involved the use of a hand needle, as opposed to method B which used an instrument technique, both methods involved handling the needle and resulted in a similar number of perforations. The great majority of perforations (84 per cent), both recognized and unrecognized, occurred in the glove that actively handled the needle, irrespective of which method of wound closure was used.

Instrument techniques that involve active handling of needles are, therefore, no less likely to cause injury than hand needles. Active handling of needles should be avoided by a meticulous non-touch instrument technique. This will probably not eliminate glove perforation (both the glove exposed to passive injury in method A and that handling the needle holder in method B were punctured in this trial), but the risk will be much reduced

Table 2 *Comparison of glove perforations between the two closure methods*

	Method A ($n=32$)	Method B ($n=28$)	
Left glove perforations	4 (1 NR)	13 (1 NR)	$P<0{\cdot}005$*
Right glove perforations	19 (10 NR)	2 (2 NR)	$P<0{\cdot}005$*
Gloves with one or more perforations‡	18 (28)	14 (25)	
Operations with one or more glove perforations§	16 (50)	14 (50)	
Skin injury (n)	0	2	
Time to close wound (min)¶	13 (7–37)	18 (5–35)	$P<0{\cdot}05$†
Time per suture (min)¶	0·63 (0·5–1·19)	0·81 (0·55–1·67)	$P<0{\cdot}01$†
Time per cm of wound (min)¶	0·57 (0·39–0·96)	0·69 (0·36–1·1)	$P<0{\cdot}01$†

* χ^2 test, † Mann–Whitney U test; ‡ number of gloves and percentage of gloves used; § number of operations and percentage of operations, ¶ median and range. NR, perforation not recognized

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Prevention of recurrent saphenofemoral incompetence after surgery for varicose veins

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Recurrence of a varicose great saphenous vein, widely attributed to failure to ligate the vein proximal to all its tributaries, is frequently observed after an accurately performed saphenofemoral ligation. However, restoration of continuity of this vein after transection in the lower thigh[1], in the groin distal to tributaries[2,3] or at the saphenofemoral junction[2,3] may develop through neovascularization. A method of limiting the extent of such neovascularization at the saphenofemoral junction is described.

Patients and methods

Three methods were successively applied to three series of patients. From each series a group of patients that had been treated 4 or more years previously was reviewed. The methods and groups are described below

Group 1

In 141 limbs of 128 patients, saphenofemoral ligation with catgut, non-absorbable silk or tantalum wire was combined with multiple ligations.

Group 2

In 127 limbs of 109 patients, saphenofemoral ligation with catgut and closure of the opening in the cribriform fascia by suture was combined with multiple ligations.

Group 3

In 268 limbs of 152 patients, saphenofemoral ligation, with the application of a patch of synthetic mesh (Mersilene®, Ethicon Ltd, Edinburgh, UK) over the saphenofemoral junction and closure of the opening in the cribriform fascia, was combined with saphenous vein stripping. Use of mesh was introduced after recurrence caused by new vessels penetrating the fascia was observed in four limbs in group 2

Patients were reviewed after 4 years for evidence of recurrent saphenofemoral incompetence (return of symptoms, palpable varices in the groin, cough impulse, positive Trendelenburg test). In all cases of suspected recurrence the groin was explored for confirmation and treatment All procedures were performed by the same investigator. The χ^2 test was used to evaluate the data.

Table 1 *Incidence of recurrence of varices at the saphenofemoral junction after surgery*

Group	Mean (range) follow-up (years)	No. of limbs	No of limbs with recurrence
1	5·4 (4–8)	141	35 (25%)
2	4·9 (4–7)	127	4 (4%)
3	5·2 (4–6)	268	3 (1%)

Results

The incidence of recurrence was lower in both group 2 ($P < 0.001$) and group 3 ($P < 0.001$) than in group 1, and there was no statistically significant difference between the incidences of recurrence in groups 2 and 3 (*Table 1*). Where recurrence was noted in association with non-absorbable ligatures or mesh these materials were found incorporated in the new vessel. In one patient a sinus, which developed owing to infected mesh, was successfully treated by excision of the mesh.

Discussion

This investigation has shown a high incidence of recurrent varices at the site of saphenofemoral ligation. It has been reported previously that restoration of continuity at the site of transection of the varicose great saphenous vein may develop through newly formed vessels[1–4] and this is consistent with the present finding that construction of a barrier of cribriform fascia over the saphenofemoral junction significantly reduced the incidence of variceal recurrence. A defect of this method was occasional recurrence due to penetration of the fascia by newly formed vessels. While reinforcing the fascia with synthetic mesh may result in a further small reduction in recurrence of the varices, the incorporation of the mesh in newly formed veins and the possibility of sinus formation are disadvantages. Silicone rubber sheeting (Dow Corning Corporation, Michigan, USA) has been in use for several years and may be preferable to mesh.

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The role of contrast radiography in presumed bowel obstruction

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A retrospective review of 229 patients with a final diagnosis of small-bowel obstruction was undertaken to evaluate the role of contrast radiography in the management of their conditions. In 84 patients (37%) the clinical findings and plain abdominal roentgenograms were sufficient for diagnosis and subsequent management. Of the remaining 145 patients with equivocal findings, 27% had an upper gastrointestinal series, 29% a barium enema, and 44% had both. Useful information (complete obstruction, unobstructed passage of contrast, or diagnosis other than adhesional obstruction) was obtained from 86% of the radiographic studies. Three patients had negative contrast studies yet eventually underwent adhesiolysis (enterolysis) and were classified as false-negative. Two patients had evidence of high-grade obstruction yet had nonoperative resolution and were classified as false-positive. The mortality in the contrast group (7%) was not statistically different than that in the no-contrast group (7%). Contrast radiography is a safe and effective means of increasing diagnostic accuracy in patients with presumed small-bowel obstruction. (SURGERY 1989;106:496-501)

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OBSTRUCTION OF THE small intestine is one of the most common surgical emergencies and may constitute up to 20% of all urgent surgical admissions.[1] The accurate diagnosis of small-bowel obstruction and the indications for conservative versus operative management, however, remain enigmatic. Despite improvements from a mortality rate of 30% to 50% at the turn of the century to 5% to 6% in recent series, an estimated 9000 deaths occur annually in the United States as a result of small-bowel obstruction.[1,2]

Classically, the diagnosis of small-bowel obstruction is based on the clinical presentation: history, physical findings, and plain abdominal roentgenography. Although this is adequate for many patients, the physical findings and roentgenograms are often nonspecific. Differentiation between simple and strangulating obstruction, between partial and complete obstruction, and between mechanical obstruction and adynamic ileus is not always possible on clinical grounds. Sarr et al.[3] demonstrated that the preoperative judgment of strangulating obstruction by senior surgeons may be correct only 48% of the time. In 1961 Silen et al.[4] and in 1978 Stewardson et al.[5] found that the "classic" findings of leukocytosis, fever, tachycardia, and localized tenderness are often inadequate for the diagnosis of gangrenous bowel.

With the demonstration of the limits of clinical acumen has come an increase in the use of adjunctive diagnostic tests. The use of contrast radiography in the diagnosis of bowel obstruction has been variably regarded as superfluous to absolutely contraindicated. Yet the use of contrast radiography in the setting of acute bowel obstruction is being reported with increased frequency.[6-8] In a series by Dunn et al.[6] 21% of 327 patients with the initial diagnosis of small-bowel obstruction underwent contrast radiography, and useful information was obtained from 50% to 80% of these studies. In order to assess the role of contrast radiography in improving diagnostic sensitivity, we reviewed our experience from January 1982 to December 1985 in patients admitted with the presumed diagnosis of small-bowel obstruction.

MATERIAL AND METHODS

Three hundred patients coded by medical records with the admitting diagnosis of small-bowel obstruction were selected for study. Of these, 229 had a final diagnosis of small-bowel obstruction based on clinical

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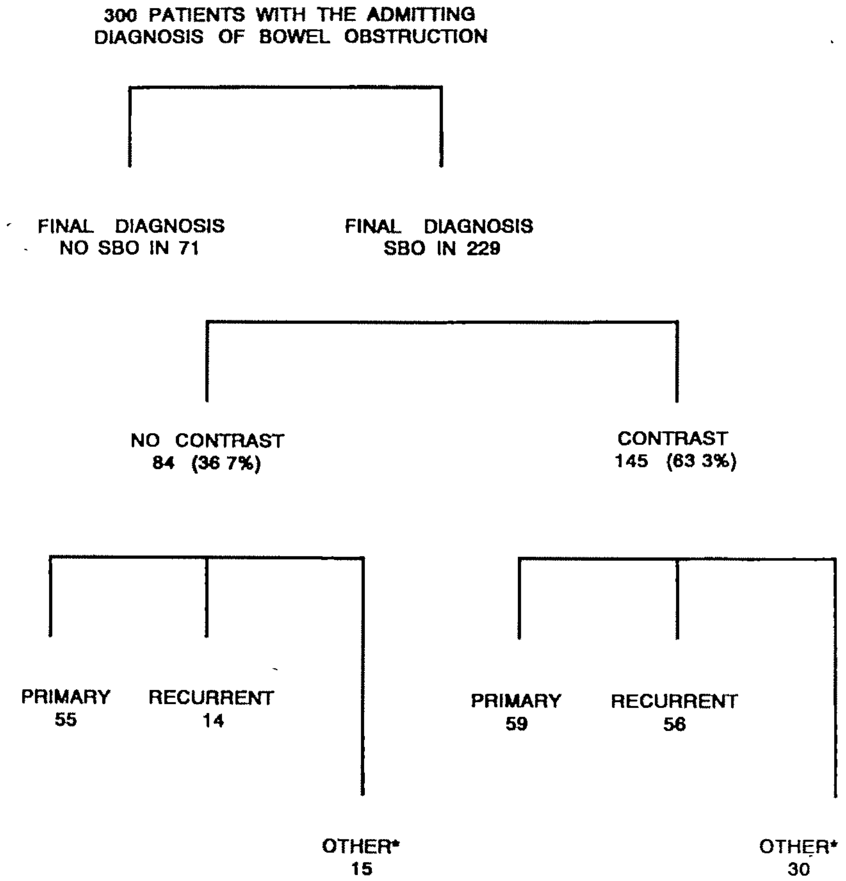
300 PATIENTS WITH THE ADMITTING DIAGNOSIS OF BOWEL OBSTRUCTION
FINAL DIAGNOSIS NO SBO IN 71
FINAL DIAGNOSIS SBO IN 229
NO CONTRAST 84 (36 7%)
CONTRAST 145 (63 3%)
PRIMARY 55
RECURRENT 14
OTHER* 15
PRIMARY 59
RECURRENT 56
OTHER* 30

* OTHER- Crohn's disease, carcinomatosis, previous abdominal/pelvic irradiation and hernias

Fig. 1. Three different subgroups of patients with final diagnosis of small-bowel obstruction.

and roentgenologic criteria, operative findings, and hospital course. The remaining 71 patients were found to not have small-bowel obstruction on further investigation. The study group for analysis was limited to the 229 patients who had a final diagnosis of small-bowel obstruction. The criteria used for the clinical diagnosis of small-bowel obstruction included bloating, obstipation, vomiting, and a history of previous abdominal surgery. In addition, all of the 229 study patients had plain abdominal films consistent with small-bowel obstruction.

In the study group 84 (37%) of the 229 patients had clinical findings and plain abdominal roentgenograms sufficient for diagnosis and subsequent management. The case histories of the remaining 145 patients in whom contrast radiography was used to confirm the diagnosis were reviewed in detail. The diagnostic workup, timing, and use of contrast studies was variable and subject to the discretion of the particular attending surgeon; on review, however, it was apparent that contrast studies were used not only in cases of atypical presentation in order to define the disease, but also in patients for whom nonoperative management of their condition woud be particularly desirable.

By convention, patients with any possibility of colonic obstruction first underwent a barium enema with attempted reflux into the terminal ileum. If this was not diagnostic, an upper gastrointestinal series with small-bowel follow-through was performed. In general, contrast studies were obtained in patients with an atypical presentation or equivocal findings on plain abdominal films. Contrast was often used to define the degree of obstruction in patients in whom operative intervention was deemed particularly hazardous (for example, patients with Crohn's disease, short-gut syndrome, disseminated carcinomatosis, previous abdominal irradiation, early postoperative bowel obstruction, and multiply recurrent adhesional obstruction).

Table I. Radiologic findings of contrast studies performed on 145 patients

Radiologic findings	*No. patients*
No evidence of obstruction	77
Low-grade or moderate obstruction	21
High-grade or complete obstruction	22
Incarcerated ventral hernia	1
Crohn's disease	8
Carcinoma/radiation changes	16
Total	145

In order to determine the role of contrast radiography in the management of small-bowel obstruction, the study group was divided into three subgroups: primary adhesional obstruction, recurrent episodes of obstruction, and "other" causes—including early postoperative obstruction, obstruction from disseminated carcinoma, inflammatory bowel disease, previous abdominal irradiation, and hernias (Fig. 1).

The retrospective nature of this study limited our ability to analyze the impact of contrast studies on clinical decision making. Nevertheless, the specific roentgenologic findings and the radiologists' interpretation of the degree of obstruction were examined.

RESULTS

Of the 229 patients with a final diagnosis of small-bowel obstruction, there were 126 male and 103 female patients, ranging in age from 11 to 102 years (mean, 62 years). The majority of these patients (63%) underwent evaluation with contrast studies, whereas the remaining 84 (37%) patients were treated solely on the basis of the clinical examination and plain abdominal films. Of the 145 patients who underwent contrast radiography, 27% had a barium enema, 29% an upper GI series, and 44% both.

Adhesional obstruction was the predominant diagnosis in this study, accounting for 80% of the 229 patients with small-bowel obstruction. Other diagnoses seen in 20% of these patients included carcinomatous obstruction, previous abdominal irradiation, Crohn's disease, and hernias. In comparing the patients who underwent contrast radiography to those that did not, the first had a higher percentage of recurrent small-bowel obstruction and "other" diagnoses. Only 40% of the contrast group were primary adhesional obstruction; 39% were recurrent obstructions and 21% "other."

The specific information obtained from contrast studies varied according to the cause of the obstruction. The radiologic interpretation of the degree of obstruction was important in the decision to pursue operative versus nonoperative management. Similarly, the cause of obstruction was often delineated by the contrast studies. Information with therapeutic significance was derived from contrast studies, as summarized in Table I. These tests supported or confirmed the diagnosis of small-bowel obstruction in 86% of the patients studied. There were two false-positives (patients with high-grade obstruction who resolved spontaneously) and three false-negatives (patients with negative contrast studies who eventually came to adhesiolysis).

The finding that contrast passed without significant obstruction supported the decision to continue conservative management. Often, radiographic findings confirmed diagnoses that merited nonsurgical management (for example, Crohn's disease, disseminated carcinomatosis, or radiation enteritis). Conversely, an interpretation of high-grade or complete obstruction prompted early surgical intervention. Twenty-two patients had these ominous findings, 17 underwent adhesiolysis, and five were treated nonoperatively. Of these five, two refused surgery, and three were not considered surgical candidates by family and attending staff. Three of the five not operated on died, and two had spontaneous resolution of their obstruction.

There was no morbidity directly attributable to the use of contrast radiography in this study. There were, however, 11 deaths (7.6%) in the 145 patients undergoing contrast studies (Table II). This group had a mean age of 75 years. Two patients refused surgery. Six of the 11 patients had adhesional obstructions, four had nonresectable cancer (two had previously undergone abdominal irradiation), and one had small-bowel incarcerated in a large ventral hernia. Two of the deaths occurred after adhesiolysis. The operative findings in these two cases were closed loop obstruction in one patient and strangulating obstruction in the other. Both patients died of sepsis. The remaining patients were considered not to be surgical candidates because of their extreme morbid states. Comparatively there was a 6% mortality rate (5 of 84) among the patients treated without contrast studies (Table II).

Forty-five patients in the contrast group underwent surgical intervention. Of these, 17 were shown by contrast radiography to have high-grade or complete obstructions. Contrast studies were negative in three patients who eventually underwent adhesiolysis.

DISCUSSION

The traditional surgical dictum of early operative intervention for small-bowel obstruction has been

Table II. Mortality related to contrast study, operative intervention, and final diagnosis

Patient	*Age*	*Sex*	*Contrast study*	*Operation*	*Final diagnosis*	*Cause of death*
1	71	M	BE	Yes	Closed loop obstruction	Sepsis
2	102	F	—	No	Small-bowel obstruction (adhesions)	Sepsis
3	97	F	BE	Yes	Small-bowel obstruction (gangrenous)	Sepsis
4	88	M	—	No	Small-bowel obstruction	Aspiration pneumonia
5	81	M	BE	Yes	Incarcerated ventral hernia	Pulmonary embolus
6	85	F	—	No	Small-bowel obstruction	Urosepsis
7	93	F	BE	No	Recurrent small-bowel obstruction	Aspiration pneumonia
8	75	M	—	No	Metastatic colon carcinoma	Abdominal sepsis
9	76	F	UGI/BE	No	Recurrent small-bowel obstruction	Pneumonia
10	66	M	BE	No	Metastatic prostatic carcinoma	Abdominal sepsis
11	52	F	—	No	Metastatic uterine carcinoma	Abdominal sepsis
12	83	M	BE	No	Recurrent small-bowel obstruction	Pneumonia
13	62	F	BE	No	Metastatic cervical carcinoma (radiation therapy)	Urosepsis
14	68	M	BE	No	Small-bowel obstruction	Pneumonia
15	54	F	UGI/BE	No	Metastatic leiomyosarcoma (radiation therapy)	Abdominal sepsis
16	56	F	UGI/BE	No	Metastatic colon carcinoma	Pneumonia

tested as clinicians have sought ways to judge the safety of expectant management. In 1984 Brolin[7] demonstrated that 88% of patients with partial small-bowel obstruction have their conditions resolve in 48 hours with conservative management. Sarr et al.[3] have estimated the risk of conservative management of complete intestinal obstruction to be 31% ± 15%. The clinical quandary, therefore, lies in our ability to differentiate between partial and complete obstruction and in assessing the signs that herald bowel ischemia and dictate abandoning conservative therapy. In this study the admitting diagnosis of small-bowel obstruction was incorrect in 23.6% of patients. This is in concurrence with Silen et al.[4] who in a review of 480 cases of small-bowel obstruction found that 41% of patients with strangulating obstruction had only one or none of the classic signs of fever, leukocytosis, localized pain and absent bowel sounds. Fully 37% of their patients with gangrenous obstruction were admitted with a diagnosis other than bowel obstruction.[4] In examining these four classic signs, Stewardson et al.[5] defined the only statistically safe circumstance for "conservative observation" as the absence of all four classic findings. None of the 41 patients with absence of all four classic findings in our study had a gangrenous obstruction.

The plain abdominal film has long been a standard adjunct to clinical diagnosis of small-bowel obstruction. Brolin[7] found the initial set of plain abdominal roentgenograms to be the most reliable predictor of outcome. By the assumption that all patients with complete obstruction will require operation and those with partial obstruction will not, the radiologist's interpretation predicted the clinical course in 86%.[7] In distinguishing mechanical obstruction from reflex ileus, Lo et al.[8] estimated that abdominal x-ray films were accurate in only 60%. In 1943 Goldman[9] demonstrated that infarcted bowel loops are seldom seen on abdominal roentgenography because they rapidly fill with blood and fluid. He postulated that a normal roentgenogram in the presence of symptoms suggesting intestinal obstruction should always raise the question of strangulation.

Of the 229 patients with small-bowel obstruction in this study, 145 (63%) underwent an upper gastrointestinal series, barium enema, or both. Useful information was derived in 85.5% (definite diagnosis, no obstruction, high-grade or complete obstruction). Although there are obvious limitations in a retrospective study, clearly contrast radiography has become a frequent clinical adjunct in the treatment of patients with presumed small-bowel obstruction at our institution. Other authors have demonstrated the diagnostic utility of these studies as ranging from 50% to 75%. Dunn et al.[6] found that 68% of small-bowel studies gave useful information, whereas 75% of contrast enemas were helpful. Lo et al. derived what they considered pertinent information from 50% of contrast studies performed. Zer et al.[10] ascribed a reliability of 68% to meglumine diatrizoate (Gastrograffin) examination in correctly determining the need for operative intervention. In our study we had two false-positives and three false-negatives in 145 patients.

Opponents of the use of contrast studies in this setting cite potential catastrophic complications. The dangers associated with aqueous contrast media (Hypaque and Gastrograffin preparations, and metrizamide) relate primarily to their physical properties of hypertonicity and potential for precipitation.[11] These agents have a tonicity about six times greater than serum. Aspiration may cause florid pulmonary edema and reflex bronchospasm. There have been reports of precipitation of water-soluble contrast material by gastric hydrochloric acid yielding a "putty-like" mass in one patient's stomach and within the balloon of another's Sengstaken-Blakemore tube.[11] Hypovolemia may occur as a result of fluid being drawn into a contrast filled viscus because of the materials' hypertonicity. This may compound the dehydration exhibited by patients with intestinal obstruction. There has been at least one report of cecal perforation in a patient with an obstructing ascending colonic lesion who was studied with water-soluble contrast material.[11] Lo et al. and Miller in cumulative series found no complications in 329 upper gastrointestinal series performed for the diagnosis of small-bowel obstruction.[8, 12]

Similarly, there have been reported complications with the use of barium sulfate in the face of bowel obstruction.[11] The incidence of complications depends on the disease entity and may take the form of obstruction, perforation, impaction, aspiration, or embolization. In a murine model Berner and Johansen[13] demonstrated that peritonitis caused by a mixture of barium and feces is more lethal than that caused by feces or barium alone. Histologically, barium in the free peritoneum produces a severe granulomatous inflammatory response.[14, 15] Perforation of a peptic ulcer during roentgenography is a known complication. Small-bowel perforation has been reported in scleroderma and other connective tissue disorders. The reported incidence of perforation during a barium enema ranges from 1/2250 (0.04%) examinations to 1/12,000 (0.008%).[11] Barium impaction tends to occur proximal to obstructive lesions but is rare in the small bowel because of the fluidity of its contents. Prolonged stasis in the gut without obstruction may predispose to impaction. Barium appendicitis has been reported as early as the ninth day and as late as 105 days after a barium enema.[11] Aspiration of barium sulfate is generally well tolerated if in small volume. Barium embolization after an upper gastrointestinal evaluation is a rare event. Several cases of venous extravasation resulting in pulmonary embolization have been reported.[11]

In this series there were no complications directly attributable to contrast radiographic examinations. The overall mortality rate of 7% in this series compares with the 4.6% to 6.7% reported by others.[2, 5, 14] The aggressive use of contrast studies may be responsible for the low incidence of strangulation obstruction and the low mortality rate (6%) in this more critical subgroup. This compares with a published mortality rate of 4.5% to 50% in patients with gangrenous small-bowel obstruction.[4] On review it appears that the use of contrast radiography led to early appropriate operation in patients with operative lesions and encouraged appropriate nonoperative management in others.

On the basis of the data from this series and a review of the literature, select groups of patients who may benefit from contrast radiography may be defined. We propose the following indications for the use of contrast radiography in the setting of presumed small-bowel obstruction: (1) to clarify the diagnosis in patients with nondiagnostic abdominal films or an atypical clinical presentation; (2) to differentiate complete from partial obstruction on the assumption that complete or high-grade obstruction is less likely to resolve and more likely to progress to gangrene, (3) to differentiate paralytic ileus from mechanical obstruction; (4) to judge the relative safety of prolonged nonoperative management, particularly in subsets of patients in whom conservative therapy would be highly desirable—(a) patients with multiple previous celiotomies for adhesional obstruction, (b) patients with the differential diagnosis of early postoperative ileus versus obstruction, (c) patients who have undergone radiation therapy, (d) patients with disseminated carcinomatosis, and (e) patients in poor general medical condition in whom increased surgical risk argues against aggressive operative therapy.

At present, we believe that the patient with the classic findings consistent with strangulation or infarction caused by acute bowel obstruction should undergo early operation. In this we subscribe to the adage that "the sun should not set on a bowel obstruction." The clinical history, physical examination, and plain abdominal films remain adequate for the diagnosis of such a typical case of small-bowel obstruction. In patients for whom the diagnosis is equivocal the judicious use of contrast radiography may be of substantial benefit in charting a therapeutic course. Our findings indicate that contrast radiography should not be viewed as delaying operative intervention but should be employed early in the clinical course to help separate those patients who will benefit from early operation from those who can be successfully treated nonoperatively. The objective is early appropriate operative therapy combined with fewer operations for failure of conservative therapy. Our data support the utility of contrast radiography as a safe, effective means of increasing the clinical accuracy in the patient with presumed small-bowel obstruction.

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Toxic megacolon and perforation caused by Shigella

Sir
We agree with the authors Gill, Feeley and Keane (*Br J Surg* 1989; 76. 796) that toxic megacolon with colonic perforation is not always due to inflammatory bowel disease but can occur in bacterial infections like *Salmonella* as illustrated by their case report. Colonic perforation in *Shigella* dysentery is rare and mainly confined to neonates[1] and infants[2]. Perforation in Bacillary dysentery in adults was reported in the Central American epidemic in 1969[3,4]. A recent case of perforation in a 73-year-old woman was reported by O'Connor and O'Callaghan[5] from Ireland. We would like to add our experience with a case of *Shigella* dysentery leading to toxic megacolon and perforation in an adult

A 68-year-old caucasian male, who had recently returned from India, presented with a 9-day history of diarrhoea with mucus but no blood, and griping abdominal pain. On admission he was dehydrated, pyrexial and had minimal abdominal tenderness in the right iliac fossa. Routine investigations were normal. A provisional diagnosis of gastroenteritis was made and he was treated conservatively Amoxycillin 500 mg three times daily was added after *Shigella flexneri* (2a) was isolated from the stool. Repeated blood cultures at various stages failed to grow any organisms. Amoxycillin was replaced by 960 mg co-trimoxazole twice daily after sensitivity results were known. After initial improvement he became unwell; plain abdominal and chest X-rays then showed free gas in the peritoneal cavity and a grossly dilated colon. A laparotomy showed friable and necrotic large bowel with perforations in three places. A subtotal colectomy (preserving the rectum) with ileostomy was carried out. Despite further intensive resuscitative measures, the patient died on the second postoperative day. The microscopic examination of the colectomy specimen showed widespread loss of mucosa replaced by very vascular granulation tissue with a thin covering of inflammatory exudate. The ulceration and subjacent inflammatory tissue extended into the bowel wall to various depths. No amoebae were identified. The slides were also reviewed for cytomegalovirus but no evidence of such infection was found.

The difficulty in distinguishing a patient with infective colitis from one with inflammatory bowel disease is well known and is described in the literature[6,7]. Inflammatory disease with concomitant bacterial infection does occur but recent studies[8,9] have shown that it is possible with reasonable certainty to distinguish inflammatory bowel disease from infective diarrhoeas on special histological features This should always be attempted if possible as preservation of rectum at the time of surgery is desirable in cases of infective aetiology.

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War wound treatments

Sir
Coupland is correct in asserting that civilian surgeons with no war surgery experience can be taught to excise wounds[1]. However, excision of all war wounds, including the common punctate through-and-through rifle wound of the extremity with minimal tissue disruption and any wound seen several days after it was inflicted, imposes an unnecessary drain on surgical resources and inflicts a higher than needed complication and morbidity rate upon the patient. His *Figure 3* shows a 6-day-old wound being subjected to 'complete wound excision ' One must wonder at the blood loss from cutting across what must be highly inflamed tissues– this appears akin to excising, rather than simply draining, an abscess Apparently, the author of this paper was following recommendations from the International Committee of the Red Cross, recently published in *Surgery for Victims of War*[2] Underlying this guidance is the flawed concept that wound excision is the only acceptable treatment for all war wounds.

Friedrich originated the idea of excising the bacteria-laden area around the contaminated wound in 1898[3] He reasoned that, if the wound could be excised *within 6 hours* of the time it was inflicted, the bacteria would be removed (since they had not yet had time to invade), the wound could be closed primarily and heal without infection LeMaitre, in World War I, practised meticulous excision of carefully selected wounds, closed them primarily, and had a wound breakdown rate of only 2·36 per cent[4]. Both Friedrich, the originator of wound excision, and LeMaitre, its most successful practitioner, are quite clear in their application of wound excision only to wounds operated upon early after the wound was inflicted They both recommended only incision as needed (to assure relief of tissue tension and assure good drainage) and leaving the wound widely open in treating wounds seen a day or more after they were inflicted.

Odling-Smee[5], reporting on civilian casualties with war wounds, wrote: 'We also adopted the "wound trimming" technique described by Ogilvie[7] which consists of the removal of foreign matter and grossly lacerated tissues and the relief of tension throughout the wound, so that any accumulation in its deeper parts should more readily escape to the surface than along muscular planes. This procedure saved a great deal of time, and brought a result comparable with the classical debridement, where careful excision is required' Odling-Smee's findings are supported by recent experimental work[6]. Additionally, Ogilvie included as his first 'Cardinal sin' of war surgery[7]; 'unnecessary operations on through-and-through bullet wounds of soft parts.' He wrote that. 'The majority of these with rest and sulfonamide heal rapidly and leave no disability, operation means loss of time and loss of function '

Wound treatment recommendations in the recently revised *Emergency War Surgery – NATO Handbook*[8] contrast sharply with the advice given in the ICRC's *Surgery for Victims of War*[2] Recommendations reflected in the *NATO Handbook* are based upon recent experimental evidence[6] as well as a thorough review of historical war surgery experience.

The preponderance of available evidence would appear to indicate that the International Committee of the Red Cross is teaching their surgical recruits a method of wound treatment that is basically contraindicated for the great majority of the wounds they are called upon to treat

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Abdominal radical total gastrectomy

Sir

The technique for abdominal radical total gastrectomy described by Chester and Gazet (*Br J Surg* 1989; **76**: 540) is not new. Immediate division of the oesophagus at the hiatus and the subsequent identification of the coeliac trunk was described by Roeder in 1933[1]. Roeder even suggested that the oesophagojejunostomy could be performed at this stage and the stomach removed 'at operation ten days later'.

We agree with Messrs Chester and Gazet that division of the oesophagus at the hiatus and development of the preaortic plane allows easy identification of the coeliac trunk and its branches, an essential step in radical gastric lymphadenectomy (R_3 resection). Whether this should be the first step in the operation is questionable. Conventional dissection[2] commences with omental detachment from the colon, followed by division of the gastroepiploic and right gastric vessels at their origin and then division of the duodenum. The spleen is reflected medially at a later stage in the procedure. Access is gained to the oesophagus from the left. This is divided and the coeliac trunk dissected as described by Chester and Gazet. This approach allows the more difficult retroperitoneal dissection to be performed later in the operation when mobilization of the stomach has improved the surgical access.

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Colorectal cancer and cholecystectomy

Author's reply

Sir

We were disappointed to read Mr Bundred's letter (*Br J Surg* 1989; **76**. 1099) as it suggests he may not have appreciated the points we were trying to get across in our paper. We have stated quite clearly that the relationship between cholecystectomy and colorectal cancer remains controversial and that the overall risk (if real) probably would not justify a screening programme.

The suggestion that our literature review was highly selected is inaccurate. A comprehensive Medline literature search was carried out and all listed papers were included in the article With regard to the two papers mentioned by Mr Bundred, the first was not published when our paper was written and the second was not listed on Medline. However, even if they had been included they would not have made a significant contribution to the debate as they are both retrospective studies with the inevitable limitations. In our paper we have stated quite clearly that such studies will not help resolve this issue The argument will only be settled by properly designed prospective studies

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Prader–Willi syndrome

Sir

Mr J.-J. Brossy advocates consideration of biliopancreatic bypass for all patients with Prader–Willi syndrome who survive to their teens (*Br J Surg* 1989; **76**: 313). He recommends this on the basis of an experience of one case. The case that inspired him to do this procedure was that of a 181 kg man with Prader–Willi syndrome who underwent jejunoileal bypass but who also suffered serious postoperative life threatening complications[1].

Mr Brossy has no grounds on which to recommend this operation in patients with Prader–Willi syndrome. Firstly, some of these patients are not obese or morbidly obese and many are not mentally retarded[2]. In a number of cases, obesity surgery is never indicated. Secondly many of the abnormalities in this syndrome, including temper tantrums and excessive daytime sleepiness, are not related to obesity and thus will not improve with weight loss[2]. Thirdly, nutritional deficiencies after biliopancreatic bypass are not uncommon as the author claims. Severe protein-calorie malnutrition is reported to be as high as 20–30 per cent and in some cases this has resulted in death. The statement that diarrhoea is seldom seen is also not true In the paper quoted it is stated that a patient with Prader–Willi syndome 'is such an aggressive consumer that the diarrhoea after intestinal bypass would probably be intolerable'[3]. Also in this paper the patients did not, as is stated, do poorly after gastric bypass. Six of seven patients with Prader–Willi syndrome lost weight and the authors comment 'that normal weight is seldom reached but that this is preferable to the risk of malnutrition'. Mr Brossy's patient was not morbidly obese, being only 34 kg over his maximum weight for height, and also did not attain normal weight losing only 20 kg which is a little over half of his excess weight.

In his operative description Mr Brossy fails to emphasize that the size of the gastric remnant is important as this has direct bearing on the amount of weight loss and the incidence of protein-calorie malnutrition It is important to understand the physiology of weight loss after this operation Scopinaro, its originator, quite clearly states that weight loss is due to the gastrectomy whereas later weight maintenance is controlled by the malabsorptive component.

Finally, 3-year follow-up is still very short and the importance of careful long term follow-up is not stressed and should be as many late complications after this procedure may develop. The recommendation that biliopancreatic bypass should be considered for all patients with Prader–Willi syndrome is unjustified, unsupported and dangerous.

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Author's reply

Sir

I did not advocate that biliopancreatic bypass should be *done* in all cases with Prader–Willi syndrome; merely considered. Clearly each case must be assessed individually and those who are not obese or mentally retarded can be treated by other means. No surgeon sees more than a handful of these cases, so one is worth reporting In my experience of some 50 cases of biliopancreatic bypass (and a similar number of gastropexies) protein-calorie malnutrition has not been a problem; nor has diarrhoea. However 10–20 per cent of patients do get anaemia (iron deficiency due to jejunal exclusion) which can be very refractory to treatment. The size of the gastric pouch was not relevant to my report Finally, the follow-up is now nearly 5 years, and the proof of the pudding is in the eating – the patient remains well and the family is delighted with the result

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Anatomical nit-picking?

Sir

Mr Scott is to be commended in his plea for a less nit-picking approach to teaching the surface markings of the deep inguinal ring (*Br J Surg* 1989, **76**: 206). It seemed to me when I was a medical student that the distinction between the midinguinal point and the midpoint of the inguinal ligament could be of little or no practical use and nothing has changed my mind since then. Mr Scott's last paragraph is entirely sensible and I hope it will comfort him to know that this is what we teach in the Royal College of Surgeons in Ireland to undergraduates and postgraduates. Students are failed no longer as a result of confusing the midinguinal point with the midpoint of the inguinal ligament

Mr Scott's pragmatic approach to the inguinal region could be taken further. Whatever the textbooks may say about the surface marking of the superficial inguinal ring, it is rarely found medial to the pubic tubercle, as even a cursory study of patients and anatomical specimens shows. The only constant feature about it is that it is superior to the pubic tubercle. Neither does the spermatic cord often pass medial to the pubic tubercle: we have several specimens in which it either overlies, or is quite markedly lateral to, the pubic tubercle as it descends into the scrotum. Anatomy does not need to be made unnecessarily complex by mystical beliefs such as these handed down from book to book and generation to generation.

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Anorectal function after abdominal rectopexy

Sir

We read with interest the paper by Yoshioka *et al.* (*Br J Surg* 1989, **76**: 64–8) on anorectal function after abdominal rectopexy and would like to concur with their findings.

In a prospective study of 6 incontinent patients with rectal prolapse studied manometrically before and after abdominal rectopexy, we have found that there is no statistically significant change in resting anal pressure after operation. Furthermore, the majority of patients obtained a marked improvement in anal continence despite a significant reduction in rectal capacity.

Our results and those of Yoshioka *et al.* would suggest that recovery of internal anal sphincter tone, as suggested by Broden *et al.*, is not the reason why continence improves after rectopexy[1]. We feel that abdominal rectopexy is a safe method for treating patients with full thickness rectal prolapse which has a low recurrence rate and provides good clinical results. The improvement in anal continence is probably related to a number of factors; we suggest that the constipation frequently encountered in patients after rectopexy plays a major role in this aspect of the functional outcome.

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1. Broden G, Dolk A, Holmstom B. Recovery of the internal anal sphincter following rectopexy: a possible explanation for continence improvement. *Int J Color Dis* 1988; **3**: 23–8

Book reviews

Diseases of the Arterial Wall

J P Camilleri, C L. Berry, J N. Fiessinger and J. Bariéty
275 × 195 mm. Pp. 693. Illustrated. 1989 London. Springer-Verlag. £216 50.

The editors and authors of this excellent textbook all work in French-speaking Europe or the UK and they are to be congratulated on a *tour de force*. This beautifully produced book covers every possible aspect of the biology and pathology of the arterial wall. It is expertly translated from (I presume) its original French, it is well documented and illustrated and it contains a most comprehensive bibliography· one chapter of 17 pages has 459 references. The references are culled not only from the conventional North American and UK literature, but also from European journals and therefore reflect the full field of published research.

This is not a book that many individual clinicians would wish to have on their shelves, but it is essential to any first class library. It fills an important gap in our understanding of the pathology of vascular disease and must represent the most up-to-date and comprehensive work on the subject. The editors and authors are to be congratulated on their gigantic effort, which has been rewarded by such a comprehensive and interesting volume

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Surgery of the Oesophagus

G. G. Jamieson. 216 × 279 mm Pp. 911. Illustrated. 1988 London Churchill Livingstone. £135 00.

The concept of oesophageal surgery becoming a specialty in its own right was perceived by R. H. Franklin when he published his classic monograph entitled *Surgery of the Oesophagus* almost 40 years ago However, few would have predicted the enormous growth of interest in oesophageal surgery and the considerable developments which have resulted in the need for this very large volume with over 100 contributors.

The book characteristically begins with sections on anatomy, physiology and investigation of the oesophagus. However, what distinguishes this volume from its competitors is the depth of detail in its coverage of the surgical management of oesophageal disease in children and adults, and particularly the comprehensive detail of operative techniques contained within its 105 chapters. In addition to the various surgical approaches to the management of such conditions as gastro-oesophageal reflux, benign structure and oesophageal carcinoma (each being discussed by an expert in that approach), there is a very useful and well illustrated section towards the end of the book on 'Techniques in Oesophageal Surgery'. Also of value is the section on management of the complications of oesophageal surgery, serving to remind us that the oesophagus is an unforgiving organ

The book is impressive in its coverage and has been well produced. Criticisms are relatively few and relate to the problems of producing such a large multiauthor volume. There is inevitable overlap in some areas and relative inequality in the degree of detail assigned to various topics, with 11 pages on Chagas' disease and a mere half page on 24-h pH monitoring. Despite the extensive detail by many authorities on the various types of antireflux surgery, it is disappointing to see so few objective data to enable the reader to make any informed choice. There is a paucity of references within the last 5 years, during which time many significant advances have been made.

Professor Jamieson has produced an authoritative and comprehensive volume which will be a useful work of reference for those surgeons who have a significant involvement with patients with oesophageal disease.

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Advances in Surgery, Volume 22

Tompkins, Balch, Cameron et al. 230 × 160 mm
Pp. 334. Illustrated. 1989. Chicago· Year Book Medical Publishers Inc. £39 50.

Most of the 11 chapters in this volume are good value. The management of liver secondaries receives a 'full-frontal' approach, but lingering doubts are nevertheless properly addressed. The obligatory chapter on AIDS is well balanced. However, the article on blood transfusion is outstanding and spells out the known as well as the potential dangers of blood products This should be required reading for anaesthetists as well as surgeons, for we should no longer accept one-unit transfusion (even if this is often increased to two units to make it look respectable), but should avoid transfusion if at all possible. There is one chapter on splenectomy for haematological disease and another on surgical aspects of lymphoma which has inevitably led to much duplication, yet mention of overwhelming post-splenectomy sepsis is confined to the references and its prophylaxis is not discussed.

The authors of the chapter on occult gastrointestinal bleeding are able to rely on arteriography for both diagnosis and treatment to an extent that is not readily available in many centres. Carcinoma of the thyroid, hepatic trauma and heart–lung transplantation are fully discussed with a sensible analysis of the controversial issues. The discrepancy in carotid endarterectomy rates between the US and the UK is enormous, but the chapter on the indications of this operation concludes that there is still a lack of adequate data Advances will come from prospective studies of medical *versus* surgical treatment, but there is no mention of a randomized trial and perhaps this is no longer possible. The discrepancy in the usage rates of Greenfield filters must be even greater than that for carotid endarterectomy and it is a pity that this issue is not given an airing

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Molecular and Cellular Mechanisms of Septic Shock

B. L Roth, T. B Nielsen and A E. McKee 155 × 235 mm. Pp. 330. Illustrated. 1989. New York Alan Liss Inc. $58.00

Like many in the series, this book is a report on the proceedings of a conference which was held in Bethesda, Maryland, in March 1988 Rapid publication has been achieved at the expense of the use of variable typefaces. All of the papers contained within the book come from American centres with 60 per cent of all authors from Bethesda The book provides an excellent update into certain aspects of current research into the pathophysiology of septic shock There is an excellent index which is commendable given that it represents the proceedings of a meeting. The papers are divided into three sections. The first deals with cellular receptors and signal transduction, in particular the recent implication of phospholipase C coupled receptors in the pathophysiology of sepsis and endotoxaemia. The second section reviews the role of endotoxin as a mediator of septic shock. This section contains a number of interesting papers, including a review of the role of lipid A analogues in the treatment of septic shock and the description of a rapid, though non-quantitative, assay for the detection of endotoxin in plasma. The final section deals with the role of cytokines in the metabolic pathophysiology of sepsis. This includes an excellent review on the effect of monokines on hepatic metabolism, including evidence for a two-way cell–cell signalling between Küpffer cells and hepatocytes.

In summary, the text provides an excellent in-depth review of certain aspects of the pathophysiology of septic shock It is perhaps surprising that little mention was made, in the endotoxin section, of the gastrointestinal tract as a source of endotoxin. The book contains little of direct clinical relevance to the practising surgeon, but will undoubtedly appeal to individuals working in the field of septic shock research, regardless of their background specialty.

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Acupuncture, Trigger Points and Musculoskeletal Pain

P E Baldry. 250 × 195 mm. Pp 308. Illustrated. 1989. Edinburgh: Churchill Livingstone £27.50.

This book sets out to summarize the history of acupuncture and to review critically several fairly recent studies which attempt to provide a scientific basis for some of the reported phenomena. This makes quite interesting reading for surgeons, especially since the myth of acupuncture anaesthesia is exposed. However, the remaining two-thirds of the volume is a recipe book, describing certain 'trigger points' which, when stimulated by the insertion of a 'dry needle', may relieve pains of musculoskeletal origin. The 'value' of this procedure is illustrated by numerous anecdotal accounts of success but it contains no instructions for relieving the sorts of pain commonly encountered in surgical practice

In summary, an interesting book to browse through while dozing in a deckchair on a warm summer afternoon, but not to be taken too seriously unless a visit to mainland China is imminent

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Pancreatic Transplantation

C-G Groth. 160 × 235 mm. Pp. 413. Illustrated 1988. Philadelphia: W. B. Saunders Company. £50.00.

This multiauthored book contains 27 chapters and is edited by a major contributor to the field. There is as yet no standard surgical procedure for pancreatic transplantation, nor is it known whether transplantation of the islets alone is sufficient. The imprecise state of knowledge is reflected in a critical chapter by the Editor which attempts to evaluate the various ways of dealing with the technical problems; for instance, should the duct be occluded by polymer or should it be drained? If so, should it be drained into the peritoneal cavity (surprisingly, this was shown to be possible), into the gut or into the bladder? Some trends can be discerned: for example, the enthusiasm for ductal occlusion has declined Diversion to the urinary tract is attracting considerable interest as it is technically easier, and analysis of the urine can warn of a reduction in exocrine secretion and the onset of rejection.

Early pancreatic transplants were performed in a similar manner to renal transplants by anastomosing the vessels to the iliac system. As a consequence, insulin is directed into the systemic rather than the portal circulation. However, using a variety of procedures, the venous effluent from a pancreatic graft can be made to drain into the portal venous system. As yet there is no clear metabolic advantage for choosing this more difficult surgical option. The perioperative and postoperative management is well documented, and postoperative complications are given special mention in separate chapters

Whether the pancreas is more or less prone to graft rejection than other organs has always been speculative. In fact, rejection is not necessarily the predominant cause of graft failure, as early technical failures are the main problem. The main thrust of work on the control of immunosuppression is now directed to the early detection of the rejection process by looking at the exocrine function which seems to be affected earlier than the endocrine function.

It is only now that there are sufficient numbers of patients surviving to determine whether there is a reduction of the pathological changes arising from the diabetic state. It is not yet possible to see whether the denervated pancreatic graft functions as well, nor whether the commonly associated renal failure adversely affects pancreatic graft function. There is a suggestion that in some patients there is a recurrent process in the graft which is similar to that producing the initial diabetic state.

There are so many unknown factors in pancreatic transplantation that we can only begin to appreciate the complexity of this promising organ transplant. Perhaps a further edition of the book will be required in a relatively short time and by then we may begin to see whether transplantation of the islets will be a better option, for there is perhaps too little emphasis on this aspect in this book.

It is, however, an excellent review of this expanding area of transplant surgery and can be warmly recommended

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Perspectives in Vascular Surgery

J. Goldstone. 260 × 180 mm. Pp 162. Illustrated. 1988. St Louis: Quality Medical Publishing Inc $165.00 (US)

This is a new and unique type of surgical publication which tries to fill the gap between the scientific research of the learned journal and the overview of the surgical textbook, which can too often be dated by the time of publication. This book is a multiple author work and, like a journal, is up to date, being published in 1988 and containing references from the same year. Like a textbook, overviews of selected topics are presented with an in-depth bibliography and the result is a work containing much clinically and scientifically useful information. An unusual feature is the deliberate variation of the layout of the articles, which include discussions of clinical topics with final comments by an Editor, descriptive articles on technique, editorial opinion on clinical problems presented by contributors, and discussions between experts on current controversies. The topics covered include lasers, concurrent aneurysm and coronary disease, reversed *versus in-situ* vein grafts, venous reconstruction, visceral ischaemia and asymptomatic carotid stenosis. With an almost all-American Editorial Board and list of contributors, it is not surprising that there is a trans-Atlantic slant to much of the opinion. Perhaps this makes it less a volume for the surgeon in training than for the established vascular surgeon. This book is Volume 1, Number 1 of a series to be published twice-yearly and is available only by subscription. It is not a book for personal purchase, although some vascular units will find it interesting to have on their library shelves.

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Clio Chirurgica Liver Transplantation

T. Starzl, C.-G. Groth and L Makowka. 280 × 215 mm. Pp. 363. Illustrated. 1988. Texas. Silvergirl Inc

This volume of *Clio Chirurgica* is a compendium of papers relating to the development of experimental and clinical liver transplantation over the last 30 years.

The development of liver grafting has been achieved only after years of dedicated laboratory work into the pathogenesis of rejection, the development of chemical immunosuppression, improvements in liver preservation and the many major technical problems involved. The historical papers which chartered this course are drawn together here in one paperback journal and the backgrounds to the important developments are briefly outlined. With so much work in the field and so many contributors, inevitably criticisms will be made of the inclusion of some and the omission of others Perhaps surprisingly, scant documentation covers the introduction of cyclosporin, something which has done so much to revolutionize immunosuppression in liver transplantation and the care of these critically ill individuals. Also, the contributions of the hepatologists, gastroenterologists and pathologists who play such a role in modern liver transplantation are not highlighted in the paper selection.

The presentation suffers significantly because so many of the papers included contain a high proportion of line drawings, diagrams and histological illustrations. Many of these reproduce poorly, are indistinct and some are frankly undecipherable. Clearly readers will need to turn to the original articles for a proper perspective; indeed, what appears here is a linking together of photocopied papers with comments, and this is perhaps disappointing given the importance and momentous changes outlined within these papers.

This compendium has its rightful place in a series devoted to collecting pioneering papers in the field of surgery, although it is likely to be of most interest to those relatively limited number of clinicians working actively in the field at this time. It is perhaps unusual, in a collection of pioneering papers, to find that the majority of authors are currently alive, and many of them are still active in the field. However, many such individuals, particularly the Europeans, may look in vain for their own contributions in this selected compendium!

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Operating Theatre Technique

R. J. Brigden. 250 × 295 mm. Pp. 968. Illustrated. 1989. Edinburgh. Churchill Livingstone. £65.00

Brigden's Operating Theatre Technique has earned the deserved place of being the standard reference text for all theatre users, theatre managers and theatre designers. Since the first edition in 1962, successive generations of theatre personnel have relied upon the information, the definition of principles, and the explanation of controversial matters contained within its pages. The fifth edition maintains previous high standards in accuracy of information, in the comprehensive coverage of the subject matter, and in the provision of clear diagrams and illustrations. The first chapter on operating department design has been revised and extended. This rightly takes into account the change in the advisory machinery through which planning processes channel medical and nursing information into project development, and highlights the change in opinion about the microbiological basis for the old tradition of clean and dirty zones The chapter on electromedical equipment, which now includes information on lasers, cryoprobes and ultrasonic apparatus, brings together information which is difficult to gather from other more specialist sources and puts it in a way that is comprehensible to theatre users It has previously been rather difficult to reproduce good colour pictures of the view seen through endoscopes or operating microscopes, but the illustrations in this edition are particularly good in this respect.

The reputation of this reference work is now so considerable that there is a danger than the information presented will be regarded as incontrovertible; where such an inexact science as medicine is concerned contrary views are always possible. Nevertheless, a balance has been struck with the benefit of 26 years of experience. The result has been that an excellent fourth edition, produced in 1980, has been succeeded by an even better fifth edition which will find its place in operating theatre suites, in teaching schools, and in the libraries of serious theatre users of every grade.

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Anorectal Malformations in Children: Update 1988

F. Douglas Stephens, E Durham Smith and N Paul. 230 × 155 mm. Pp. 620. Illustrated. 1988. New York. Alan Liss Inc $150.00.

In this tome, the Editors are assisted by 13 contributors of international repute, each having made important advances in the treatment of infants with anorectal malformations.

The clinical photographs are good, but those of operative procedures serve no useful purpose. Some of the illustrations are so small that they are difficult to understand The reproduction of radiographs is adequate, but it is confusing to have diagrams of operations interspersed in the text describing different procedures. Two classifications of the more common anomalies are offered; a third is then offered for rarer lesions which does not fit into either class!

Relatively few pages, about 3 per cent, are devoted to somewhat optimistic short-term results, and the problems of the incontinent teenager are barely mentioned. I was astounded to see paediatric surgeons recommending the use of suppositories and petroleum emulsion for constipated children. Ultrasonography of the perineum is discussed, but not illustrated, and although pelvic CT scans are said to be of increasing importance, only nine badly reproduced 'cuts' demonstrate the point.

The book suffers from the problems associated with multiauthorship There is repetition from one chapter to another, with some contributors offering conflicting advice. Some operations are described in varying ways by different contributors. The book would have benefitted from judicious editing, which could have reduced its length by at least a third

As a reference work, the book is unique. The comprehensive list of references, from 1543 to 1987 inclusive, is of value in itself but in an 'update' I had not expected to find 'Reproduced with permission of the publishers' on over a third of the pages. Perhaps 'all that there is' has been included, but I had expected more

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Reconstructive Microsurgery

B McC. O'Brien and W. A. Morrison. 285 × 225 mm. Pp. 540. Illustrated. 1987. Edinburgh: Churchill Livingstone. £120.00.

The senior author, Mr Bernard McC O'Brien, is internationally respected as the father of modern microvascular surgical techniques. He has for many years been ably supported by Wayne Morrison who, similarly, is known for his original contributions to this specialty. At the Microsurgical Research Centre in Melbourne, surgeons from all over the world have learnt the basic techniques of microvascular surgery, and how to apply them in the transfer of skin, muscle, bone, nerve, tendons and many other tissues. The first book by Mr O'Brien, *Microvascular Reconstructive Surgery*, was published in 1977 and had only one chapter devoted to free flap surgery. Over the last 12 years, an explosion in this form of transfers has occurred and the new book requires some 20 chapters to cover the subject. The unit in Melbourne has been the forerunner of placing microvascular and microneural repairs on to a proper scientific basis. They have explored many methods of transferring tissues, and have examined the pathological results. Many of the techniques have already been described in the journals, either published by themselves or by others. Clearly the authors have tried these various procedures and are in a good position to describe the advantages and pitfalls of them.

Reconstructive microsurgery is a fascinating field which is constantly developing and therefore any book like this is unlikely to be absolutely up to date. The presentation of the work is clear and concise, with intelligent use of illustrations The reference literature is meticulous and particularly helpful, as the bibliography pertaining to this subject is widespread, only recently having an international journal of its own. The particular strength of the book is that it is the experience of a single unit following the growth of a specialty from its earliest development to the present time. It does not rely on multiple authors and is therefore much less uneven and more readable. It is really the best publication of its type and is essential for any surgeon interested in this field of surgery. It will form an excellent basis for the next development in this field, which must be the transplantation of these tissues to another individual.

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Atlas of Advanced Surgery

M. S. Litwin 310 × 235 mm. Pp 198. Illustrated. 1986. London Yorke Medical Books £60.00.

For the general surgeon interested in gastroenterology, this slim 200-page volume neatly fills the gap between publications devoted to basic techniques of standard operations and the multivolumed works covering all the specialties. The Editor has chosen a team of authors, each of whom is an expert in his field, who have either designed or perfected the operation they describe, but a firm editorial hand has maintained a uniformity of style throughout. The emphasis is on clear illustrations of operative procedures and the text has been kept to a minimum, assuming a basic knowledge on the part of the reader. Most of the more major and complicated procedures in gastrointestinal surgery are described, but there are one or two surprising omissions in oesophageal and colorectal surgery. For example, although replacement of the oesophagus with colon is described, three-stage oesophagectomy with gastric reconstruction is not included. Only one form of ileal pouch–anal anastomosis is described. A minor irritation is the tendency to use eponymous titles for instruments instead of a functional description. In a few instances pyloroplasty is illustrated in a misleading way, although, in general, the illustrations are excellent. In the description of low anterior resection, taking down the splenic flexure is felt to be only occasionally necessary; many surgeons would disagree with this and would regard it as an important step in the procedure However, these are minor criticisms and this book succeeds admirably in its purpose I recommend it to all general surgeons with an interest in gastroenterology.

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Surgery for General Practitioners

B. Maurice. 220 × 140 mm. Pp. 264. Illustrated. 1989. London: Castle House Publications Ltd. £15.00.

Brian Maurice has written a book based on lectures given to general practitioners. It behoves all general surgeons to be aware of this book in the light of current proposals to improve services to patients. There are a number of good arguments both for and against general practitioners performing certain minor operative procedures in their surgery. Given motivation and appropriate training, however, there are certain socioeconomic advantages to one or two general practitioners in large group practices undertaking a central role in the performance of specific operations.

The author makes the point that 'there is no place for a general practitioner to do the occasional minor operation', and clearly and concisely explains everything that a dedicated general practitioner needs to know to perform more than 20 operations under local anaesthetic in their own surgery. He has enlisted the help of a consultant anaesthetist who covers the subject of local anaesthesia, with or without sedation; maximum recommended dosages for three common agents are given. Early treatment for problems is emphasized and the reader is told, in no uncertain terms, that facilities to deal with circulatory arrest must be readily available.

The book is full of sound advice and warnings of the pitfalls to be avoided, reflecting the general surgical experience of the author. Criticisms that I made while reading this pithy volume were, on reflection, subjective and based on anecdotal experience.

The chapters on instrumentation, suture materials and stitching are easy to follow, and I would recommend them for any doctor in training who is involved in performing minor surgery. Even those general practitioners who elect to refer their patients to hospital would benefit from reading the chapters on specific operations and treatment of postoperative complications.

In these days of increasing specialization and controversial White Paper proposals, this book fills an important niche and is welcomed unreservedly.

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Clinical Thinking in Surgery

E A. Sterns. 180 × 260 mm. Pp 642. Illustrated. 1988 East Norwalk: Appleton and Lange. £24 50.

This is a most welcome and interesting addition to the large number of available textbooks of surgery. It is intended for the medical student and aims to set out the relationship between the basic sciences (particularly of anatomy, physiology and pathology) and clinical thinking It emphasizes the basic science and then presents clinical material in the form of illustrated cases that represent common clinical situations. The author aims at a coverage comprehensive enough for the needs of the average medical student, but which is limited to the entities that are both common and particularly valuable in illustrating the logic of treatment

After a chapter on approaches to the solution of surgical problems, the material is arranged in four sections· the first covers general problems such as wound healing, infection and shock, the second is a very comprehensive section on regional problems; the third section is about trauma and burns; and the fourth section discusses preoperative and postoperative care.

The style is attractive, being readable and enjoyable, crisp and clear, and at times challenging and exciting. The illustrations, mainly line drawings, are clear although many are not original. There is an appendix which discusses how to conduct a literature search and this is indeed a welcome feature The format is attractive with double columns and, while it will not fit into a white coat pocket, it is a very manageable paper-covered volume. British medical students will, I believe, find it more to their taste than most of its trans-Atlantic rivals.

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A Colour Atlas of Human Dissection

C. C Chumbley and R. T. Hutchings. 100 × 120 mm Pp 160 Illustrated. 1988. London· Wolfe Medical Publications. £14.95.

This book offers 'a scheme of practical anatomy' It is lavishly illustrated, hence the title, and the photography is excellent. Dissection instructions are brief and it is suggested that they be used in tandem with another colour atlas: page and *Figure* references to the McMinn and Hutchings atlas are cited. It is evidently intended in the first place for students beginning their anatomy course rather than postgraduates, e.g those students studying for the FRCS primary examination.

I think that junior students will have difficulties with this book (postgraduates to a lesser extent). First, they are committed to the extra expense of buying another atlas. If the photographs in the present atlas had been labelled, it would have been cheaper for the student.

Second, the order of dissection (some surface anatomy and osteology are included) of parts starts with the most difficult region: head and neck, upper limb, thorax, abdomen and pelvis, and upper limb. However, the teachers may elect to start where they wish

Third, there are the usual problems where a brief simple approach is attempted. Thus there may not be enough information for the inexperienced student to locate and identify the structure he is ordered to find. In some photographs a structure is clearly indicated by, for example, forceps, but there are several examples (mostly 'close-ups') where even the experienced eye would have difficulty in orientating the picture relative to the body, let alone identifying the required structure. In addition, the brief format seems to me to induce a divorce between structure and function. Surely there are no better places than in the dissecting room and in a dissecting manual to explain function. What would be the point of painstakingly dissecting the origins and insertion of the sternocleidomastoid muscle and the course of the spinal accessory nerve if the student is not told or asked to deduce what the muscle does and that this nerve supplies it?

I believe that some modifications are required to make a second edition more useful to the student. The publishers are, however, to be congratulated on a technically well produced book.

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Notices and announcements

12–17 November 1989
International College of Surgeons 16th European Federation Congress
Jerusalem, Israel
Information: Professor Arye L. Durst, The Secretariat, PO Box 983, Jerusalem, Israel

15–17 November 1989
Fourth EORTC Symposium on Advances in Gastrointestinal cancer: Research and Treatment
Strasbourg, France
Information: J. P. Arnaud MD CMCO, 19 rue Louis Pasteur, Schiltigheim BP 120, 67042 Strasbourg Cedex, France

16–19 November 1989
3-D Imaging in Medicine
San Diego, California, USA
Information: Ms Janice Ford, CME Coordinator, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19104, USA

17–19 November 1989
Eighth Annual Trauma Symposium
El Paso, Texas, USA
Information William Beaumont Army Medical Center, El Paso, Texas 79920, USA

18–22 November 1989
9th Biennial Asian Congress on Thoracic and Cardiovascular Surgery
Taipei, Taiwan, Republic of China
Information: The Secretariat, The 9th Biennial Asian Congress on Thoracic and Cardiovascular Surgery, PO Box 68–439, Taipei, Taiwan, Republic of China

23–24 November 1989
Annual General Meeting of the Vascular Surgical Society of Great Britain and Ireland
Dundee, UK
Information· Mr James Forrester, Department of Surgery, Ninewells Hospital, Dundee DD1 9SY, UK

26 November–1 December 1989
Gynaecological cancer: new perspectives
London, UK
Information Courses Dept., The British Council, 65 Davies St , London, W1Y2AA

30 November–1 December 1989
Drug Delivery & Drug Targeting Systems, Latest Advances
London, UK
Information· Renata Duke, IBC Technical Services Ltd., Bath House (3rd Floor), 56 Holborn Viaduct, London EC1A 2EX

3–9 December 1989
Breast Cancer: New Developments in Biology, Diagnosis and Treatment
London, UK
Information· Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, UK

5–7 December 1989
4th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr Joseph W C. Leung, Department of Medicine, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

10–15 December 1989
Osteoarthritis of the knee, aetiology, management and recent advances
London, UK
Information: The British Council Courses Dept, 65 Davies Street, London W1Y 2AA

17–22 January 1990
Introduction to Endocrine Investigations
Newport Beach, California, USA
Information: Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

19–21 January 1990
26th Head and Neck Course
Liverpool, UK
Information: Professor P M. Stell, Dept of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, UK

20–21 January 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

28 January–8 February 1990
The Biological Basis of Radiotherapy
London, UK
Information. The British Council, Courses Dept, 65 Davies Street, London W1Y 2AA

4–9 February 1990
HIV and AIDS: Management and Control
London, UK
Information· The British Council, Courses Dept, 65 Davies Street, London W1Y 2AA

4–10 March 1990
Cancer in Children
London, UK
Information The British Council, Courses Department, 65 Davies Street, London W1Y 2AA, UK

11–13 March 1990
2nd Surgical Masterclass of the Royal College of Surgeons of Edinburgh
Aviemore, UK
Information. Mrs Maureen Webb, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

19–29 March 1990
Advances in Neurosurgery
Glasgow & Edinburgh, UK
Information: Courses Department, The British Council, 65 Davies St, London W1Y 2AA

28–30 March 1990
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Cardiff, UK
Information· The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

1–6 April 1990
Clinical Genetics
Cardiff, UK
Information British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

29 May–1 June 1990
Peripheral Vascular Disease
London, UK
Information: The British Council, Courses Department, 65 Davies St, London W1Y 2AA

5–9 June 1990
European Association for Gastroenterology & Endoscopy: European Digestive Disease Week
Vienna, Austria
Information: Mondial Congress, Faulmanngasse 4/11 A-1040 Wien, Austria

11–14 June 1990
6th International Congress on Breast Diseases
Boston, Massachusetts, USA
Information: 6th International Congress Secretariat, c/o Office of Continuing Education, Tufts University School of Medicine, 136 Harrison Avenue, Box 36, Boston, MA 02111, USA

13–16 June 1990
5th European Symposium on Gastrointestinal Motility
Augsburg, FRG
Information. Professor M. Weinbeck, Dept. of Internal Medicine III, Zentralklinikum, D-8900 Augsburg, FRG

20–23 June 1990
Annual Meeting of The Endocrine Society
Atlanta, Georgia, USA
Information· Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

24–29 June 1990
The 3rd Oxbridge Organ Transplantation Course
Oxford, UK
Information. British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

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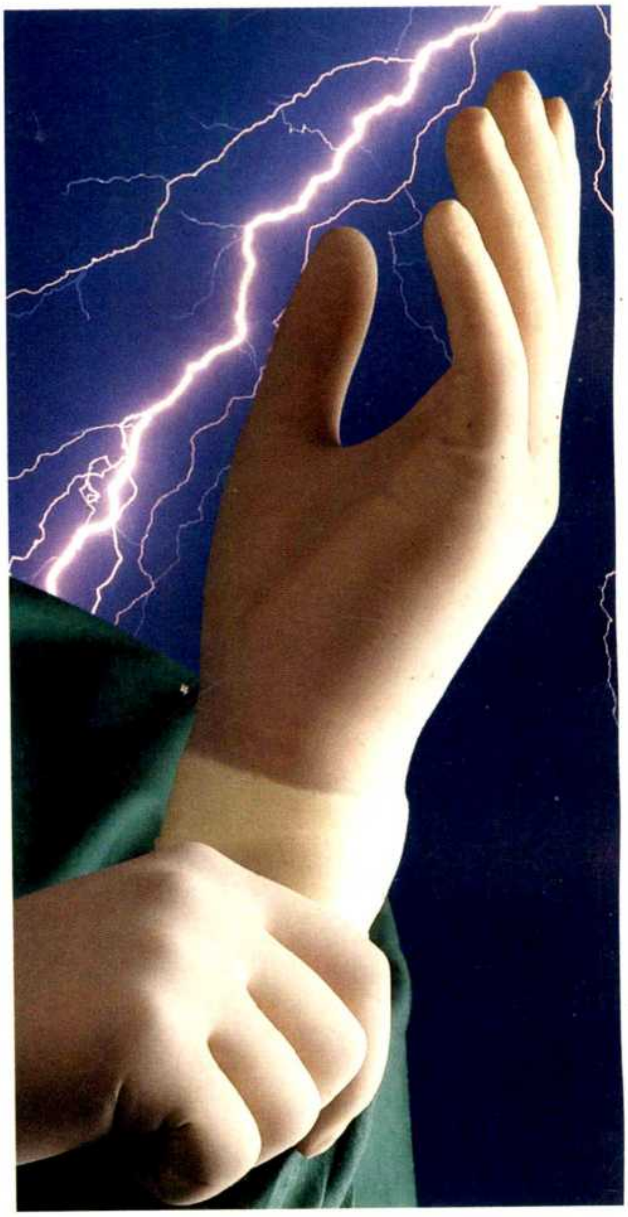

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PDS and PDS II (Polydioxanone) Monofilament Synthetic Absorbable Sutures are prepared from the polyester poly (p-dioxanone). The empirical molecular formula of the polymer is $(C_4H_6O_3)n$. PDS (Polydioxanone) sutures are coloured by adding D & C Blue No. 6 during polymerisation. PDS II (Polydioxanone) sutures are coloured by adding D & C Violet No. 2. PDS II sutures may also be manufactured undyed (clear). PDS and PDS II (Polydioxanone) are available attached to stainless steel needles of various types and sizes, and are sterilised by ethylene oxide gas.

PDS and PDS II (Polydioxanone) sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action: Two important characteristics describe the in-vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass. The general mechanism by which in-vivo degradation of polydioxanone occurs is hydrolysis.

Data obtained from implantation studies in rats show the following absorption profile:

14 days post implantation –
    70% strength remaining
28 days post implantation –
    50% strength remaining
56 days post implantation –
    14% strength remaining

This indicates a significantly longer period of wound support than previously available with an absorbable suture.

The absorption or loss of mass is minimal until about the 90th post implantation day and is essentially complete within 180 days.

Uses

PDS and PDS II (Polydioxanone) monofilament sutures are intended for use where an absorbable suture or ligature is indicated. They may have particular application where longer wound support is required. See strength retention data above.

Dosage and Administration

By implantation.

Contra-indications, Warnings, etc.

These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required or in conjunction with prosthetic devices e.g. heart valves or synthetic grafts.

The safety and effectiveness of PDS and PDS II (Polydioxanone) sutures in neural and cardiac tissue have not been established.

As with all monofilament synthetic sutures, care should be taken to ensure proper knot security.

Conjunctival, cuticular and vaginal epithelium sutures could cause localised irritation if left in place for longer than 10 days. Superficial placement of subcuticular sutures may also be associated with erythema and reaction during the course of absorption.

Pharmaceutical Precautions

Recommended storage conditions are below 25°C, away from moisture and direct heat. Shelf life is 5 years, the expiry date is shown on each pack. Do not re-sterilise the contents of the pack. Unused product from opened packs should be discarded.

As with all sutures, care should be taken to avoid damage when handling. Avoid the crushing or crimping application of surgical instruments such as needle holders and forceps to the strand, except when grasping the free end of the suture during an instrument tie.

Legal Category

Not applicable.

Package Quantities

PDS is available in various lengths in gauge sizes Metric 0.2 to 0.4 (10/0 to 8/0). PDS II is available in various lengths in gauges sizes Metric 0.5 to 5.0 (7/0 to 2). The sutures are packaged in sealed aluminium foil packs and peel apart overwrap pouches. The sales unit is a film wrapped box containing 12 or 24 packs.

Further Information

No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

Product Licence Nos.

0508/0020 PDS II – Undyed
0508/0021 PDS II – Violet Dyed
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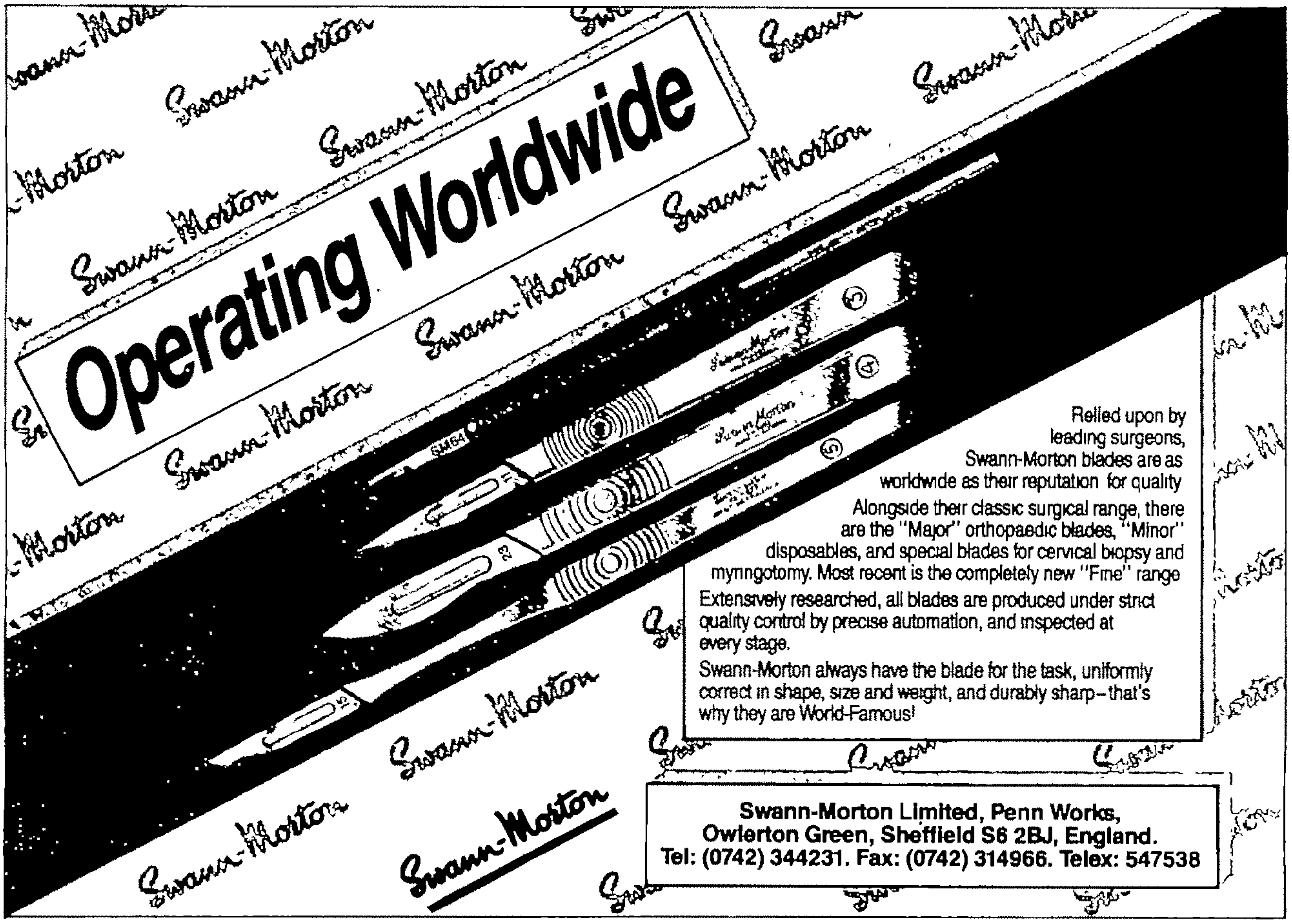

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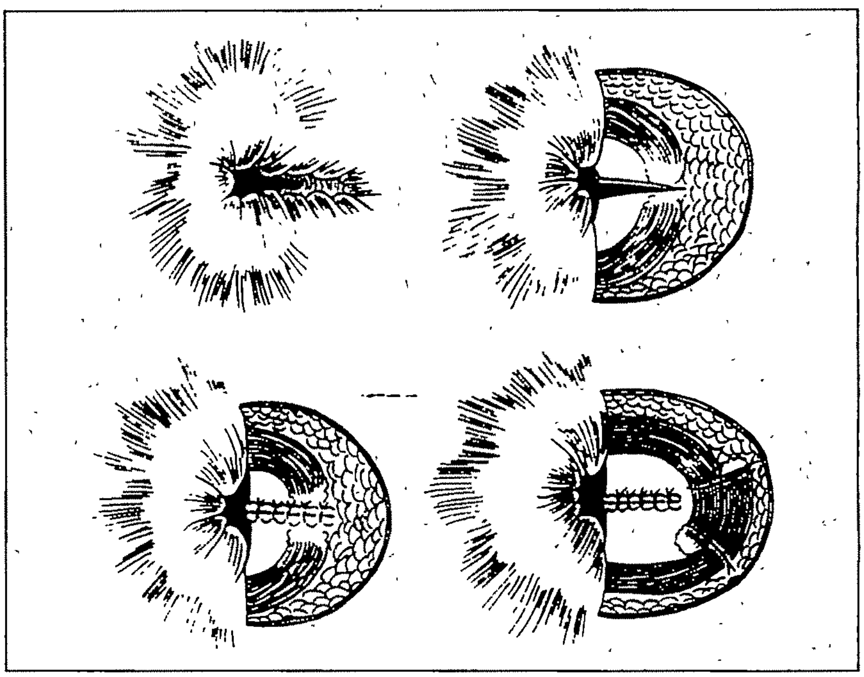

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Gastric cancer: different diseases

Worldwide, gastric cancer remains a leading cause of death from malignant disease. Over the last 50 years, an abundance of literature has accumulated on this disease, highlighting fascinating features concerning the behaviour of a malignancy. Different patterns of disease have evolved to the extent that it has been suggested that the disease in Japan is different from that in the West. More recently, it has become clear that different therapeutic strategies may produce different end results. However it is not clear whether these reflect innate biological differences in tumours or are the result of different treatments.

In the Western world, there has been a significant decline in the incidence of gastric cancer. This is most marked in the United States, but is now being seen in Europe. While still the most common cause of death in Japan, a similar trend has been observed there. Recently, it has been reported that the location of the tumour within the stomach itself is changing. The antrum remains the most common site, but there has been a significant increase in the proportion of lesions at the cardia[1].

Certain clinico-pathological features of the disease have been established that facilitate international comparisons. In all countries, stage I disease is associated with a good prognosis. It is of interest that the Japanese report a survival rate of 98 per cent at five years for patients with tumours of this stage, but most studies from Europe report a five-year survival rate of 70 per cent. This suggests a difference in biological behaviour of these types of tumours in the East and West. However, a paper[2] from the British Society of Gastroenterology indicates that the differences may be in classification rather than behaviour. In a review of 132 early gastric cancers the survival at five years of true early cancers was 95 per cent, but in those which have been reclassified the survival rate is similar to that reported in other studies[3], many of which were retrospective and not subject to pathological review. The Lauren pathological classification[4] has identified two tumour types of different biology, namely intestinal and diffuse. The former is associated with a better prognosis and is more common in areas with a high incidence of the disease. It is also the type of tumour that decreases in frequency with a fall in gastric cancer incidence. Thus, on currently available evidence, tumours do appear to behave differently in the East and West but when comparisons are made between like tumours the results are similar.

A further explanation for different results may lie in management. The Japanese have an aggressive diagnostic policy which has resulted in an increase in the detection of 'early' disease, curable by surgery. Although screening programmes are unlikely to be cost-effective in the West, early diagnosis in high-risk groups has been shown to increase the proportion of early lesions to 20 per cent. Mucosal gastric cancers are symptomatic in 50 per cent of cases and thus, endoscopic diagnosis of dyspeptic patients over the age of 40 is recommended. From this group, patients with mucosal changes such as dysplasia (and possibly atrophic gastritis and metaplasia) are selected for regular follow-up.

Surgery is the treatment for early stage disease and once again the major advances have come from Japan. Two features are of particular note. Firstly, the operative mortality rate in the United Kingdom for total gastrectomy is often in excess of 20 per cent[3]. Specialist centres report figures in the range 1–5 per cent[5]. Results of this kind can only be achieved by the acceptance and development of specialist groups. Secondly, the extent of the surgery is variable and its benefits debatable. The Japanese approach has been to perform extended radical gastrectomy (R2). However, the literature from the West does not support the case that this type of surgery is of benefit and the issue is currently the subject of a Medical Research Council trial.

Consideration must be given to the role of other methods of treatment for gastric adenocarcinoma. Recognition of the importance of early diagnosis and surgery as the prime areas for advance has resulted from the failure of other potential methods of treatment. Disappointingly, cytotoxic chemotherapy has been of no therapeutic benefit and there is no place for its use outside clinical trials[6]. However, the stomach is an endocrine end organ and stomach cancer may yet prove to be a hormone responsive tumour; an exciting development has been the reported[7] benefit of treatment with the H_2-receptor antagonist cimetidine.

In conclusion, there is now strong evidence that gastric cancer may occur in different biological forms, that there are changing patterns of disease, and that diagnostic and therapeutic strategies may influence the long-term results. It is these features which produce the apparent differences between East and West and which hold the key to future advances in management.

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Br. J. Surg. 1989, Vol. 76, December, 1228–1229

Ambulatory hernia surgery

In the United States ambulatory hernia surgery became a fact of life when Medicare, the federal programme that reimburses hospitals and physicians for medical care of the elderly, finally followed the lead of other third party payers and disallowed reimbursement for hospitalization of those over 65 years old undergoing elective inguinal hernioplasty. This dictate was less Draconian than it first appeared because nearly all groin hernioplasties were already being performed preferentially on a day-patient basis. This timely method of performing inguinal hernioplasty benefits everyone. It is safe, convenient, efficient, economical and very popular. Furthermore, the mere idea of ambulatory hernia surgery softens the emotional impact of the operation and thereby reduces disability by encouraging the patient to get on with his life. In the beginning, financial incentives were necessary to promote acceptance. However, it soon became obvious that the majority of the patients preferred not to be admitted as in-patients.

Making ambulatory hernia surgery easy and unintrusive for the patient is primarily the responsibility of the surgeon. Of course, ambulatory units must be user-friendly, but in the end how the patient 'does', as measured by disability, morbidity, and chance of recurrence depends almost solely on the technical skills of the surgeon, the hernioplasty employed, the mode of anaesthesia and attention to minute details. These important matters for concern have been largely overlooked. They need addressing for they define good surgery.

Ambulatory hernia surgery does not preclude general, spinal or epidural anaesthesia. However, the perfect anaesthesia for a primary, reducible inguinal hernia in the non-obese is local anaesthesia. In routine cases, the assistance of an anaesthetist is usually not necessary and only adds to the cost. Furthermore, local anaesthesia eliminates the need for costly preoperative testing. Informed patients actually prefer local to general anaesthesia and like to have the operation without missing their morning cup of coffee. Surgeons ought to like local anaesthesia because it shortens the time between cases and challenges their technical ability. Local anaesthesia is safe, and furthermore it allows immediate ambulation and early discharge from the ambulatory unit. Much has been written about the technique of administering the anaesthetic. However, the comfort of the patient has more to do with the surgeon's ability to operate gently and to dissect sharply than it has to do with his technical skills with a syringe and needle filled with local anaesthetic.

The burning pain caused by the administration of the local anaesthetic can be eliminated by neutralizing the agent. This also greatly enhances the anaesthesia and reduces the quantity of anaesthetic required. The 8·4 per cent sodium bicarbonate solution from the operating room emergency tray may be used if vials of small quantity are not available. The pH of plain local anaesthetic is about 6.0, and simply drawing 1 ml of the sodium bicarbonate solution into a 10 ml syringe filled with 9 ml of plain local anaesthetic brings the pH to a comfortable value of about 7.5. The pH of local anaesthetic with adrenaline is about 4.0 and therefore 2.5 ml of the sodium bicarbonate solution are required.

The selection of the hernioplasty is important. If other things are equal, the hernioplasty producing the least disability ought to be the procedure of choice. The hernioplasty with the reputation for the shortest convalescence is the Shouldice hernioplasty. In fact, it was E. E. Shouldice who, more than 45 years ago, pioneered short stay hernioplasty and thus paved the way for day hernia surgery. He held the view, long before other surgeons concurred, that patients could not wilfully hurt themselves. Acting accordingly, he discharged his patients after a couple of days and encouraged them to resume all physical activities as soon as their discomfort permitted. This attitude, coupled with a low chance of recurrence, brought many thousands of patients to his Toronto clinic. The hernioplasty developed at his hospital by co-workers Obney and Ryan actually complements this attitude. The Shouldice hernioplasty's good results have been confirmed by many and are attributable to the use of continuous sutures which distribute tension evenly, to the imbrication of the structurally important innermost aponeurotic–fascial layer resulting in a strong seam, and to a repair which is essentially tension free[1–3]. The operation is easy and is a joy to perform. What remains astounding is how many surgeons still disbelieve the good results and stubbornly adhere to techniques which do not match the Shouldice hernioplasty and are less well suited for day surgery.

Most patients with bilateral hernias can have them repaired at the same time provided that the hernias are not too large and that the time for the awake patient on the uncomfortable operating room table is not too long. There is no advantage in separating the procedures and patients are disappointed at the thought of two separate periods of disability. Surprisingly, the disability from bilateral hernioplasties is not essentially different from that of unilateral hernioplasty. However, a prudent surgeon would delay repair of a second indirect hernia if for any reason the indirect sac of the first side had to be completely dissected from the cord. This occurs with sliding indirect inguinal hernia sacs.

Morbidity prolongs convalescence and disappoints patients. However, the belief that

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hospitalization will protect the patient from complications, promote sound wound healing, and reduce the chance for recurrence has no basis in fact for primary inguinal hernia surgery. Morbidity begins in the operating room. It cannot be overemphasized that expeditious, meticulous, precise dissection reduces discomfort, minimizes complications and promotes primary healing. In general drains should be avoided and dead space eliminated. Haemostasis must be complete and achieved without necrosing the tissues excessively with the electrosurgical unit or by mass ligation. The overwhelming desire of assistants to draw up tightly sutures which approximate tissue must be assiduously avoided. Even the skin closure is important. Steri-Strips (3M, St. Paul, Minnesota, USA) are ideal. They are quick to apply, painless, removable by the patient, promote healing, and reduce the chance of infection. Steri-Strips do not pinch the skin closure and are therefore not haemostatic. Patients may be alarmed by skin bleeding which saturates the wound dressing. This drawback can be prevented by supplementing the Steri-Strips with a subdermal monofilament suture of very fine absorbable synthetic material.

Ischaemic orchitis and its sequel, testicular atrophy, angers men of all ages and invariably produces litigation. It is caused by thrombosis of the spermatic cord induced by dissection trauma to the pampiniform plexus and is not owing to the tightness of the deep ring reconstruction or some occult genital infection as some surgeons have speculated[4]. The complication can be minimized by careful sharp dissection of the cord (never blunt), limiting dissection of the spermatic cord to the inguinal canal only, and avoidance of dissection in the distal portion of indirect inguinal hernia sacs whenever possible.

Recurrent hernias and hernias associated with connective tissue disorders are at high risk of recurrence following repair. Most of them are manageable in ambulatory hernia centres, and for success a prosthesis is advisable. Approaching these difficult hernias by the preperitoneal route has several important advantages. One advantage is the obvious fact that the preperitoneal space is the ideal site in which to implant the prosthesis. The preperitoneal approach also eliminates dissection of the previously mobilized, scarred and splayed spermatic cord and, for all practical purposes, avoids the complication of testicular atrophy. Finally the preperitoneal approach exposes all of the anatomy of the posterior wall of the groin and allows the surgeon to implant a large prosthesis which can extend far beyond the sutured, or sometimes even unsutured, myo-aponeurotic defect in the abdominal wall.

A useful technique which facilitates implantation of a prosthesis in the preperitoneal space is parietalization of the spermatic cord[5]. The technique consists of dissecting the peritoneum away from the elements of the spermatic cord. The vas deferens and testicular vessels will then lie against the wall of the pelvis and the prosthesis can cover them and the deep ring completely. This makes a slit in the mesh to accommodate the cord unnecessary. The secret of successful prosthetic hernioplasty is to make the mesh sufficiently large. The currently popular repairs using patches and plugs of mesh are often inadequate because the prostheses are too small and hernias return through adjacent areas of weak tissue. Recently, promising techniques have been described[6,7]. For ambulatory repair the best access to the preperitoneal space is through a unilateral transverse incision centred over the rectus muscle 2–3 cm below the bispinous line but well above the deep ring. General anaesthesia is usually necessary because of the extensive dissection. Despite the dissection, patients experience very little postoperative discomfort, perhaps because the large prosthesis provides support.

The development of ambulatory hernia surgery is a great step forward. The results, however measured, are very surgeon dependent. If done correctly and carefully, patients will be grateful and appreciative and society will benefit by freeing up limited hospital resources for the critically ill.

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Local low dose intra-arterial thrombolytic therapy: the risk of stroke or major haemorrhage

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The use of local low dose thrombolysis is gradually increasing. Most experience is with streptokinase, although newer agents such as recombinant tissue plasminogen activator (rTPA) may offer more effective lysis with reduced complications. We have reviewed the experience documented in 19 prospective series published between 1974 and 1988 in an attempt to define the incidence of stroke, major haemorrhage and minor haemorrhage. The overall risk of stroke was 1·0 per cent of patients (14 cases). Major haemorrhage occurred in 5·1 per cent of patients (71 cases) and minor haemorrhage occurred in 14.8 per cent (92 out of 620 cases). There was little difference between the two thrombolytic agents, although the experience with lower doses of rTPA suggests it may offer a reduced risk of haemorrhagic complications. It is essential that all studies concerning thrombolysis should give their exclusion and inclusion criteria in full to allow an accurate appraisal of haemorrhagic complications, with the hope of improved patient selection and reduced morbidity in the future.

Keywords: Thrombolytic therapy, peripheral vascular disease

Interest in peripheral arterial thrombolysis is increasing. The great advance was the realization that comparatively low doses (5000 units h^{-1}) of streptokinase[1] could achieve an increased success of thrombolysis when administerd via an indwelling intra-arterial catheter, compared with conventional systemic thrombolytic therapy (100 000 units h^{-1})[2]. Since this report, a variety of agents and doses have been used in attempts to improve thrombolytic success further, and to achieve a reduction in the incidence of haemorrhagic complications.

In published series exclusion and inclusion criteria for thrombolytic therapy are difficult to evaluate as they are often not given[1,3,4–8], or are inexact, such as 'recent CVA' (cerebrovascular accident)[3,9]. Some use a limit of 'less than 2 months history of CVA'[10–12] or 'less than 12 months history of CVA'[13–15]. The National Institutes of Health Conference[12] suggested that a history of a stroke within the preceding 2 months is an absolute contraindication but made no further recommendation. A history of a previous embolic stroke is no absolute safeguard in thrombolytic therapy. In a prospective series of patients with acute stroke in whom embolus accounted for 31 per cent of presentations[16], 5 per cent of the total developed intracranial haematoma, confirmed by computed axial tomography and/or angiography. In addition, differing post-thrombolysis drug therapies (aspirin, dipyridamole, heparin, warfarin) make an accurate determination of haemorrhagic risk difficult to assess. Monitoring of fibrinolytic parameters, in particular plasma fibrinogen levels <100 mg ml^{-1}, may help to predict incipient haemorrhage. In this way Totty[17] may have avoided significant haemorrhage in three patients, whose fibrinogen levels fell to <100 mg ml^{-1}, by treating them with cryoprecipitate.

We have reviewed the experience with peripheral arterial thrombolysis in 19 prospective series published between 1974 and 1988. Early papers have been omitted from the analysis where a later report exists, to avoid overlap of clinical material.

Clinical experience

Nineteen series dealing with local low dose intra-arterial thrombolytic therapy, published between 1974 and 1988, and involving 1401 patients have been reviewed[1,3–21]. The majority of series describe experience with the use of streptokinase (1224 patients) with only 177 patients receiving intra-arterial recombinant tissue plasminogen activator (rTPA). The usual dose of streptokinase was 5000 units h^{-1}, although some centres used up to 10 000 units h^{-1}, as a continuous low dose intra-arterial infusion. The dose of rTPA, however, was rather more variable as is to be expected in initial trials with this drug. Doses used varied from 0·25 mg h^{-1} (Reference 10) to as high as 10 mg h^{-1} (Reference 15). The later reports confirm that the lower doses appear as efficacious as the higher doses[12,14,15]. Care should be taken in comparing the relative risks of the two agents as none of these reports is a randomized comparison of these agents and experience with rTPA is still limited and its dose regimens are still being evaluated.

For the purposes of this review, major haemorrhage has been defined as haemorrhage requiring transfusion, or causing hypotension, or requiring specific treatment in the form of fresh frozen plasma, cryoprecipitate or antifibrinolytic drugs. Minor haemorrhage has been defined as any other haemorrhage not requiring specific replacement therapy or transfusion and not causing hypotension. Such haemorrhage was usually in the form of a small or moderate sized haematoma around the point of entry of the catheter.

Stroke

There was a total of 1401 patients in the collected series, 14 (1·0 per cent) of whom suffered a haemorrhagic stroke. Of these, 11 occurred after streptokinase therapy (*Table 1*) and three after rTPA (*Table 2*). There was no statistically significant difference between the drugs in this report. It is impossible to estimate

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Table 1 *A collected series of 1224 patients receiving low dose intra-arterial streptokinase*

Reference	Year	No. of patients	Dose (units h^{-1})	Concurrent heparin (units h^{-1})	CNS exclusion	No. of patients with.		
							Haemorrhage	
						Stroke	Major	Minor
Dotter[1]	1974	17	$1–10 \times 10^3$	No	—	0	1	5
Berni[3]	1982	6	5×10^3	No	—	0	1	—
		10	5×10^3	300–500	—	1	2	—
Totty[17]	1982	21	5×10^3	No	Recent CVA	0	2 + (3)*	
Becker[4]	1983	48	5×10^3	Variable	—	1	6	14
Hurley[5]	1984	34	$3–19 \times 10^3$	—	—	2	11	8
Mori[6]	1983	45	5×10^3	250–800	—	1	4	15
Katzen[7]	1984	65	5×10^3	in 10 only	—	0	6	—
Graor[8]	1985	151	5×10^3	No	Recent CVA	1	7	8
Kakkaseril[9]	1985	35	$5–10 \times 10^3$	No	—	0	6	7
Walker[18]	1985	26	$5–10 \times 10^3$	No	CVA	0	3	0
Lammer[19]	1986	136	$2·5 \times 10^3$	$2·5–7·5 \times 10^3$	—	0	5	—
Comerota[20]	1987	34	$5–10 \times 10^3$	No	Intracranial disease	2	0	2
Earnshaw[10]	1987	32	5×10^3	250	CVA <2 months	0	0	5
Hess[21]	1987	564	1×10^3 (2 min)	No	—	3	5	—

* Cryoprecipitate given; –, not stated; CVA, cerebrovascular accident. Patients with a previous history of cerebrovascular accident were excluded

Table 2 *Collected series of 177 patients receiving intra-arterial recombinant tissue plasminogen activator*

Reference	Year	No. of patients	Dose (units h^{-1})	Concurrent heparin	CNS exclusion	No. of patients with:		
							Haemorrhage	
						Stroke	Major	Minor
Graor[13]	1986	33	$0·05–0·1 \text{ mg kg}^{-1} \text{h}^{-1}$	No	CVA <1 year	1	1	3
Earnshaw[11]	1987	23	$0·25–2·5 \text{ mg h}^{-1}$	No	CVA <2 months	1	4	3
Risius[14]	1987	21	$0·1 \text{ mg kg}^{-1} \text{h}^{-1}$	No	CVA <1 year	0	3	2
		19	$0·05 \text{ mg kg}^{-1} \text{h}^{-1}$	No		0	0	2
Berridge[12]	1988	15	$0·5 \text{ mg h}^{-1}$	No	CVA <2 months	0	0	4
Verstraete[15]	1988	50	10 mg h^{-1}	Variable	CVA <1 year	1	1	8
		16	$3–5 \text{ mg h}^{-1}$	–		0	0	6

* Cryoprecipitate given; –, not stated; CVA, cerebrovascular accident. Patients with a previous history of cerebrovascular accident were excluded

Table 3 *Risk of stroke or haemorrhage from thrombolytic therapy*

Group	No. of patients	No. of strokes	No. of major haemorrhages	No. of minor haemorrhages
Overall	1401	14 (1·0)	71 (5·1)	92 (14.8)*
Streptokinase	1224	11 (0·9)	62 (5·1)	64 (10·3)*
rTPA	177	3 (1·7)	9 (5·1)	28 (15·8)

Values in parentheses are percentages. * Four series[3,7,19,21] do not report incidence of minor haemorrhage and have been excluded

how many haemorrhagic strokes would have occurred naturally as there are no placebo groups available.

Major haemorrhage

Major haemorrhage occurred in 71 (5·1 per cent) patients overall: in 62 following streptokinase therapy and in 9 following rTPA. Again, there is no statistically significant difference between the drugs.

Minor haemorrhage

Minor haemorrhage usually occurred as a haematoma around the catheter entry site. This affected 92 patients overall (*Table 3*). Streptokinase therapy resulted in 64 patients with minor haemorrhage. Four series[3,7,19,21] were not included in these figures as they did not report the incidence of minor haemorrhage. Minor haemorrhage following rTPA affected 28 patients.

There is no obvious advantage in terms of reduction of haemorrhagic complications from the use of the relatively fibrin specific rTPA and, indeed, there is no statistically significant difference between the two agents with respect to any of the complications studied. However, it would be wrong to draw too many conclusions on the comparative safety of rTPA compared with streptokinase on the basis of this review, as the results for rTPA include all the early work when doses were still comparatively high. Recent experience with lower doses is considerably more favourable. Of the 177 patients (*Table 3*) who received rTPA, the last 61 received much lower doses without any stroke occurring and with only one patient experiencing major haemorrhage.

Discussion

The risks following peripheral local low dose arterial thrombolytic therapy are difficult to assess owing to the plethora of differences in methodology between different centres. Nevertheless, we do need to have some perspective on the risks of haemorrhage and, in particular, stroke, not only to allow adequate informed consent, but also to compare these risks with those following either the systemic use of thrombolytic agents or surgery. Analysis of published data in terms of total dose of lytic agent used is meaningless owing to the relatively short half-lives of these agents and the variation in duration and route of administration.

Previous use of intravenous streptokinase in high doses (100 000 units h^{-1}), following a loading dose of 1 250 000 units, produced lysis in only one-quarter of patients[2]. In the same study major haemorrhage occurred in 18·8 per cent of patients and was 'probably the cause of death' in 7 per cent. Strokes occurred in 5·9 per cent of patients. This report has been referred to by Aldrich *et al.* who inexplicably only mention three haemorrhages and two strokes[22].

In an attempt to reduce the frequency of haemorrhagic complications and stroke, while achieving a high thrombolytic success rate, the search continued for more fibrin specific agents. Acetylated streptokinase complex was developed. Initial animal studies appeared promising but when it was used as an intravenous thrombolytic agent, the incidence of haemorrhagic complications was unacceptably high and the success rate of lysis was poor[23]. Tissue plasminogen activator showed considerable fibrin specificity, however it was initially available only in small impure quantities from human uterine[24] or Bowes melanoma cell lines. Highly purified TPA was subsequently produced from this cell line allowing the gene of TPA to be cloned[25]. This led to the development, using genetic engineering, of recombinant tissue plasminogen activator (rTPA) which was soon found to have the same fibrin specificity and thrombolytic properties as the natural substance[26]. Fibrin bound plasminogen activates rTPA and circulating inhibitors such as α-2-antiplasmin prevent or at least reduce its systemic activation. Despite comparatively low local doses, a progressive systemic response is still seen with streptokinase (at a dose of 5000 units h^{-1} after 4 h) and with rTPA. However, with the latter it is both delayed and significantly reduced[27].

Clinical experience with rTPA in peripheral arterial thrombolysis is still limited. The published reports so far highlight the disparity in techniques, doses, exclusions and indications between different centres. However, in all centres using rTPA the recommended doses are becoming lower. Graor *et al.*[13] initially used 0·1 $mg\,kg^{-1}\,h^{-1}$, and have subsequently shown that 0·05 $mg\,kg^{-1}\,h^{-1}$ is equally effective[14]. Similarly, Verstraete *et al.*[15] reported a multicentre series, initially using 10 $mg\,h^{-1}$. Reduction of this dose to 5 $mg^{-1}\,h^{-1}$ and then 3 $mg\,h^{-1}$ in their own centre does not appear to have reduced the success of the procedure. In Nottingham[11], a small study with doses between 0·25 and 2·5 $mg\,h^{-1}$, showed that effective lysis could be achieved with even lower doses. We have followed up this with a further series using 0·5 $mg\,h^{-1}$ and have achieved a success rate of 74 per cent for thrombolysis, without major haemorrhagic complications or stroke[12].

It is illogical to assume that the most fibrin specific 'ideal' agent will be free from all risk of stroke and haemorrhage. Patients will continue to have silent strokes and asymptomatic or unrecognized peptic ulceration in association with a haemostatic platelet/thrombus plug. The 'ideal' agent must recognize this as a legitimate target and will lyse this plug as readily as it will the peripheral arterial thrombus it was intended to treat. The relative maturity of the two different sites will determine if and when the complication will occur. For example, when thrombolytic agents are used in the presence of Dacron® (Du Pont) grafts, massive haemorrhage occasionally ensues. These grafts may take many years to become completely sealed with a neointima and, in the meantime, part of their integrity relies on thrombus incorporated in the interstices of the graft material. If the dose of lytic agent is either high enough, or is administered for long enough, lysis of the lining thrombus occurs with the formation of a permeable graft[28,29]. Whether the 'ideal' agent is administered systemically or locally via an indwelling intra-arterial catheter will have some bearing, as in the latter case thrombus prevents the flow of blood distally into the run-off or collateral vessels, such that only small amounts of the lytic agent will escape into the main circulation and cause lysis of distant thrombus.

Patient selection has a major role to play in reducing the complication rate associated with this technique, but exclusion criteria must not be so strict that patients who may benefit from this form of therapy are denied it. Those who are at greatest risk from conventional treatment (previous strokes, ischaemic heart disease, chronic obstructive airways disease, acute peripheral arterial thromboses), are the ones who should be considered for peripheral arterial thrombolysis as an alternative therapy.

The wisdom of the concurrent use of heparin remains uncertain. Some investigators use a low dose infusion to attempt to reduce the incidence of pericatheter thrombosis. Others use higher doses to achieve an activated partial thromboplastin time approximately double that of the control. Some do not use it at all. The augmentation of lytic effect, associated with higher doses of heparin[30], does not occur with lower dose schedules, but the newer low molecular weight heparin fragments may offer enhancement at much lower doses[31]. It has been shown that a systemic effect is produced using low dose streptokinase after as little as 4 h[26] and it might seem that heparin would only add risk without any advantage. The question should be answered by current trials.

In conclusion, the overall stroke rate following low dose peripheral arterial thrombolysis is 1·0 per cent, with a 5·1 per cent risk of haemorrhage requiring transfusion and/or correction with coagulation factors. We must await the completion of further trials using the newer agents such as rTPA to determine if they offer a lower incidence of complications when used at lower doses. All reports concerning the use of thrombolytic agents in peripheral arterial thrombolysis should clearly state the exclusion criteria used and should discuss the complications found in relation to the risk factors, as suggested at the National Institutes of Health conference[32]. Only then will we be able accurately to assess the risk posed by peripheral arterial thrombolysis with different agents. There is insufficient information given in the published studies to determine whether any previous history of stroke should be regarded as an absolute contraindication for this form of therapy.

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Serum enzymes and other laboratory tests in acute pancreatitis

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This review evaluates selective enzymes and blood tests available for the diagnosis and prognosis of acute pancreatitis. It is concluded that serum amylase and lipase measurements represent the best available diagnostic methods. Newer alternative assays still require careful evaluation

Keywords: Acute pancreatitis, diagnosis, prognosis, amylase, lipase, enzymes, plasma markers

Acute pancreatitis still represents a major diagnostic and therapeutic challenge. Not only is the diagnosis controversial and often unsatisfactory in the emergency setting, but also the severity of the disease is often underestimated as suggested by McMahon *et al.*[1], who pointed out that only one out of three severe cases of acute pancreatitis is recognized to be severe at an early stage of the disease. Wilson *et al.*[2] recently reported that 42 per cent of their fatal cases of acute pancreatitis did not have a correct diagnosis prior to necropsy.

The determination of serum amylase is the basis for definition of acute pancreatitis in practically all studies[3]. Most cases lack surgical or post-mortem confirmation, thus it is possible that the frequency of the diagnosis is overestimated or underestimated in many series. Only recently have non-invasive techniques, such as contrast-enhanced computed tomography (CT) scanning using high resolution, fast, third or fourth generation scanners enabled direct visualization of the pancreas and its surroundings; such CT scans represent to date the most accurate method of diagnosing acute pancreatitis[3–5]. During the acute phase of the disease CT scanning is far superior to ultrasonography[5] and even perhaps to laparotomy[6]. CT scanning, however, is not always available and cannot be performed in all instances where acute pancreatitis is suspected clinically because of its high cost[4]. The purpose of the present paper is to review the value of enzymatic markers and some other selective tests and to propose guidelines with which to establish the diagnosis and severity of acute pancreatitis.

Amylase

Total serum or plasma amylase

Determination of total serum amylase remains, for most investigators, the cornerstone of the diagnosis of acute pancreatitis since this enzyme is universally regarded as the most practical and sensitive single screening test[3,7]. Amylase is an enzyme with a molecular weight of about 50 000 Da[7,8] found in the blood for the first time in 1846 by Magendie[7] and first measured quantitatively in animals by Foster in 1867[9]. Its importance in pancreatic disease was suggested in 1909[10] and its role in acute pancreatitis definitively demonstrated by Elman *et al.* in 1929[11]. More than 200 methods of determination of serum amylase have been described[7,8]. The most common of these are the amyloclastic (e.g. Wohlgemuth, Nephelometry) and the saccharogenic methods (e.g. Somogyi) and, more recently, methods using dye substrates (e.g. Russel, Phadebas) and chromogenic substrates[7,8]. However, no international reference method has yet been adopted and since various substrates are used, comparison of amylase determinations between different centres is often hazardous.

Plasma amylase is believed to rise within 24 h of the onset of acute pancreatitis[7,12,13], initially as a result of direct venous drainage of the pancreas and its peripancreatic tissue and later by lymphatic drainage through the thoracic duct[14]. The role of the transperitoneal absorption of the enzyme in increasing the plasma level is probably less important than previously reported[15,16]. Return to normal values is generally noted within 5 days[7,8,12,13]. Normalization can sometimes occur very rapidly, indicating early resolution of the disease or, less frequently, extensive destruction of the pancreas with cessation of pancreatic amylase production[17,18]. The 'threshold' diagnostic level of serum amylase is often arbitrarily chosen and varies considerably from one study to the next, ranging from one to nine times the upper reference value[17]. Higher levels tend to enhance diagnostic specificity by eliminating false positive results; this, of course, is to the detriment of the diagnostic sensitivity of the enzyme. To evaluate the specificity of total serum amylase, Weaver *et al.*[19], through the use of isoamylase determinations, have shown that 18 out of 57 cases of hyperamylasaemia associated with abdominal pain were, in fact, not due to acute pancreatitis. Koehler *et al.*[20] reported similarly that ten of 37 patients with a clinical diagnosis of acute pancreatitis and hyperamylasaemia had incorrect diagnoses in that the elevated serum amylase originated from extrapancreatic tissue. Indeed, about one-third of the cases of hyperamylasaemia and abdominal pain are in fact not due to acute pancreatitis, giving a diagnostic specificity for serum amylase approaching 70 per cent[3]. Abnormal levels of serum amylase are secondary to increased production or decreased catabolism, as can occur in renal failure[21] and in liver dysfunction[22]. However, renal impairment alone has little effect on serum amylase concentrations since in such situations 75 per cent of amylase is metabolized via an extrarenal mechanism, possibly involving the reticuloendothelial system[8,13,23]. The list of non-pancreatic conditions accompanied by hyperproduction of amylase is constantly increasing (*Table 1*).

The sensitivity of serum amylase in acute pancreatitis is extremely difficult to evaluate since most authors have based the definition of the disease on the hyperamylasaemia itself, resulting in a very low incidence of normoamylasaemic acute pancreatitis. Only some cases found incidentally during surgery or autopsy are occasionally mentioned in the literature and represent commonly less than 5 per cent of all acute pancreatitis cases[17]. In rare studies and small series, the incidence of normoamylasaemic acute pancreatitis can exceed 10 per cent[48]. Spechler *et al.*[49] noted a normal amylase level on admission in 32 per cent of 68 cases of acute alcoholic pancreatitis. This exceptionally high rate of normoamylasaemic acute pancreatitis was further questioned since in only two-thirds of these cases was the diagnosis supported by ultrasonography or CT scan findings[50]. Recently, using systematic early CT scanning to ascertain the clinical diagnosis of acute pancreatitis, irrespective

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Table 1 *Hyperamylasemia not related to acute pancreatitis*

Cause	References
Abdominal	
Biliary tract disease	(7, 24, 25)
Perforated peptic ulcer	(7, 15)
Acute perforated appendicitis	(7, 26, 27)
Peritonitis	(25, 26)
Intestinal obstruction	(25–27)
Afferent loop syndrome (probably via oedematous or necrotic gut)	(26, 28)
Mesenteric infarction	(27, 29–30)
Liver diseases	(22)
Aortic aneurysm dissection	(25)
Pregnancy	(31)
Ruptured ectopic pregnancy	(32)
Prostatic disease	(33)
Pancreatic cancer	(34)
Ovarian neoplasm (P-type)	(35)
Thoracic	
Myocardial infarction	(7, 36)
Pulmonary embolism	(7, 36)
Pneumonia	(36, 37)
Metastatic carcinoma of the lung	(7, 37–39)
Breast cancer	(40)
Postoperative	
Abdominal operations	(7, 41, 42)
Non-abdominal operations	(7, 36, 41, 42)
Trauma	
Cerebral trauma	(7, 43)
Burns and traumatic shock	(7, 43)
Metabolic disorders	
Diabetic ketoacidosis	(44)
Drugs	
Opiate	(7, 36)
Oxyphenbutazone and phenylbutazone (probably via parotidis)	(45)
Others	
Renal transplantation	(46)
Bisalbuminemia	(47)

of level of serum amylase, one of the present authors found an incidence of 19 per cent of normoamylasaemic acute pancreatitis[17].

Isoamylase

Measurement of amylase isoenzymes has been attempted to improve the clinical specificity of the total amylase[21,51–53]. α-Amylase is an enzyme that acts on starch to split α-1–4 glucosidic bonds randomly. It is found in humans and in animals, while β-amylase is specific to plants[7,54]. In humans, electrophoretic techniques enable the distinction between the two main types of isoamylases: pancreatic type (p-type, AMY 2) and salivary type (s-type or AMY 1). Their respective fractions in the blood vary among individuals[53–55]. However, normally, pancreatic amylase represents about 40 per cent of total amylase and is quite specific to the pancreas[51,54]. Recently, three different kinds of p-isoamylases have been differentiated by electrophoresis, of which the p-3 fraction has been noted to be the most specific for AP[55,56]. Conversely, salivary amylase is totally non-specific and is found in all tissues that contain amylase[7,27,37,51]. Finally, an electrophoretically atypical amylase termed 'Y-type' has been isolated and found to be associated with some carcinomas[54].

Isoamylase determination has little if any value in enhancing the diagnostic sensitivity (i.e. when amylase level is normal the preponderance of p-type isoamylase rarely unmasks acute pancreatitis), although some authors have found it to be of use in cases of slight hyperamylasaemia[51,53]. Its major advantage resides in the important boost in specificity allowing differentiation between pancreatic and extrapancreatic isoamylase[51,53,55,56]. As mentioned above, recent clinical studies have shown that isoamylase profiles can change the diagnosis of acute pancreatitis in up to one-third of hyperamylasaemic patients[19,20]. However, conditions other than acute pancreatitis, especially abdominal emergencies (such as mesenteric infarction, intestinal obstruction and perforated peptic ulcer) and some cancers (e.g. ovarian neoplasm) are occasionally associated with p-type hyperamylasaemia[27,35]; in such circumstances isoamylase profiles will not distinguish acute pancreatitis from these conditions.

The method used for isoenzyme determinations is of critical importance: whereas a number of accurate electrophoretic and chromatographic techniques have been validated, the currently popular rough approximation based on differential inhibition of s-type isoamylases by a wheat protein inhibitor is probably less reliable[53,57–59]. In the emergency setting isoamylase determination is rarely used since efficient measurements are often time-consuming[3,17,60], however new rapid tests should still be evaluated for their ability to enhance the diagnostic accuracy of total amylase.

Macroamylase

Amylase bound to an abnormal protein to form a high-molecular complex was first described by Wilding *et al.* in 1964[61]. The analysis of isoenzymes has revealed that both p-type and s-type isoamylase could be incriminated. The binding protein can be an IgG as well as an IgA[62,63], and the molecular weight of this complex ranges from 150 000 Da to more than one million Da; a molecule too large to be excreted by the kidney[61–63]. Thus, the characteristic of macroamylasaemia is an elevated plasma amylase in the absence of elevated amylasuria. A similar presentation could theoretically be encountered in conditions other than macroamylasaemia such as renal dysfunction[63]. An amylase:creatinine clearance ratio (Cam:Ccr) of less than 1 per cent has been proposed as pathognomonic of macroamylasaemia[64]. However, a normal Cam:Ccr does not exclude macroamylasaemia – as is the case when the ratio for serum activities of macroamylase to normal amylase is low[63]. Isolated hyperamylasaemia accompanied by normal values of other pancreatic enzymes (e.g. lipase) should alert the clinician to the possibility of macroamylasaemia. However only appropriate and specific laboratory measurements can ascertain the presence of macroamylase[65].

The prevalence of macroamylasaemia in the normal population occurring as a persistent or transient event ranges between 1 and 2 per cent[63,66], representing a benign chemical derangement that has not yet been consistently correlated with any particular disease[7,63,66]. Macroamylasaemia has been incriminated in 6–28 per cent of patients with chronic hyperamylasaemia of unknown origin[57,67]. In acute pancreatitis, macroamylasaemia has been found in no more than 3 per cent of the cases[63,66].

Serum amylase and hyperlipidaemia

Lipaemic serum has been reported in up to 20 per cent of cases of acute pancreatitis associated with alcohol abuse[68,69]. In such situations, hyperamylasaemia is often difficult to evaluate. The hyperlipidaemia interferes with the amylase assay leading to a spuriously normal result; plasma triglycerides either suppress or inhibit serum amylase activity[51]. The spuriously normal amylasaemia usually can be unmasked by serial dilutions of the plasma[51,68,69], although this simple method is not universally accepted[70]. Cam:Ccr ratio has been found to be less influenced by hyperlipidaemic serum and an elevation of the ratio was considered useful in making the correct diagnosis[51]. On the other hand, lipaemic serum represents a difficult diagnostic problem in acute pancreatitis regardless of whether hyperlipidaemia is secondary to pancreatitis or the cause of it, since the presence of hyperlipidaemia is often undetected before the pancreatitis episode[68–70].

Urinary amylase

Determination of amylase in urine has sometimes been considered to be more accurate than serum amylase estimation, and was selected by some authors to support their diagnosis of acute pancreatitis[71,72]. Although rising slightly later, hyperamylasuria commonly parallels hyperamylasaemia, and the same limitations of specificity and sensitivity therefore apply[3,7]. The clearance of amylase or the estimation of the rate of urinary amylase output is subject to errors inherent in difficulties of collection[71]. Furthermore, amylase is unstable in urine and unpredictably variable results are obtained from stored samples[73]. A recent rapid colorimetric test for urinary amylase (Rapignost®, Behring Werke, Marburg, FRG) has been found to be as accurate as any other enzyme determination in the diagnosis of acute pancreatitis in the emergency setting[74,75]. The test can be readily performed by medical or nursing staff over a 3-min period and is extremely easy to interpret and could represent the method of choice for the screening of the disease. However, other studies comparing the results obtained by the Rapignost amylase test with the measured serum amylase level were less encouraging with some false positive results and a sensitivity which was estimated to be less than 70 per cent[76,77].

Amylase/creatinine clearance ratio

The Cam:Ccr ratio was first proposed by Levitt *et al.* in 1969 as a means of detecting the increase of amylase clearance rate during acute pancreatitis[78]. Amylase passes through the glomerular membrane and, under normal conditions, approximately 75 per cent of the filtrate is reabsorbed in the proximal tubule. The clearance of p-type isoamylase is higher than that of s-type, but the magnitude of the difference remains controversial[23,79]. The immediate advantage of the Cam:Ccr ratio determination over the direct clearance measurement is the absence of the need for accurate urine volume collection, and short collection time, thus permitting a 'spot or catch' urine sample to be of value[7]. However, it is difficult to achieve true simultaneity between blood and urine sampling in common nursing practice.

The normal ratio is approximately 2 per cent and an increase above 6 per cent has been proposed as diagnostic of acute pancreatitis[79,80]. The sensitivity of this ratio was first considered as excellent since it was thought that in the presence of normal amylasaemia a normal ratio excluded the diagnosis of acute pancreatitis[79]. Subsequently, Warshaw *et al.*[80] emphasized that the increase of the ratio was specific for acute pancreatitis; no false positive values were recorded in 44 cases of hyperamylasaemia not related to pancreatic disease. Later on, the usefulness of Cam:Ccr ratio in acute pancreatitis diagnosis was questioned by several investigators and its value is now generally considered to have been overestimated[3,42,71,81,82]. Cases of acute pancreatitis with a normal ratio were reported[64,81] and a number of causes other than acute pancreatitis were associated with a high ratio, namely the postoperative period[42,82], diabetic ketoacidosis[83], burns[83,84], cancer of the pancreas[83,84], perforated peptic ulcer[83,84], haemoglobinuria[85], acute yellow atrophy[84], low plasma amylase level[86], and some cases of renal failure[21]. Thus, according to more recent data, the Cam:Ccr ratio seems to have little value in its diagnostic sensitivity and specificity for acute pancreatitis, and seems to be merely a component of non-specific tubular dysfunction similar to that found in cases of proteinuria[3,87]. However, as mentioned above, there are situations in which it might be useful to calculate the Cam:Ccr ratio such as cases of hyperlipaemic serum, macroamylasaemia, and renal failure[21,88].

Amylase and aetiology of acute pancreatitis

Generally speaking, higher amylase values have been reported in cases of acute biliary pancreatitis than in pancreatitis due to other causes[7,8,17]. Hiatt *et al.*[89] recently showed that the amylase curve profile was significantly different between alcoholic and gallstone pancreatitis. In the latter group, the initial serum amylase value was higher, the final value was lower, and the decline in daily values was more rapid. According to Gullick[90] it is probable that the magnitude of the hyperamylasaemia in pancreatitis is at least partially related to the degree of ductal obstruction and inversely proportional to the degree of acinar secretory failure. Cases of biliary disease without evidence of pancreatitis such as choledocholithiasis, cholecystitis and ruptured gallbladder[7,24,91], have occasionally been associated with high values of serum amylase, reaching up to ten times the upper reference levels. However, in these cases the absence of acute pancreatitis has rarely been demonstrated with certitude.

Alcohol is sometimes associated with asymptomatic hyperamylasaemia[92]. In some series, up to 24 per cent of chronic alcoholic patients without evidence of pancreatitis presented with an increase in serum amylase concentration[36]. Of cases of hyperamylasaemia due to alcohol consumption 44–87 per cent have been found to have a predominance of s-type isoamylase and damage to the parotid gland has often been incriminated[92,93]. On the other hand, the acute ingestion of large quantities of alcohol in non-alcoholic subjects has no effect on plasma amylase[7]. Among the numerous other substances that have been reported to induce hyperamylasaemia it is often not clear whether the amylase is of pancreatic or other origin. However, some drugs have been clearly proved to induce pancreatitis (*Table 2*).

During endoscopic retrograde cholangiopancreatography (ERCP) hyperamylasaemia was noted in 25 per cent of the cases the following morning, but only 3·5 per cent of the patients suffered from abdominal pain and fewer than 1 per cent had documented acute pancreatitis[101]. In another series, an increase in amylase levels was noted in 43 per cent of patients including 4 per cent of those with clinical evidence of acute pancreatitis[102].

In trauma, amylase determination is of little value in terms of diagnostic sensitivity or specificity[103]. An increase in serum amylase concentration is seen in approximately two-thirds of cases with blunt abdominal trauma[43,103] and is often not related to pancreatic lesions. Non-abdominal trauma including thoracic and head injury is often associated with hyperamylasaemia[43]. Isoenzyme determination does not help any further in determining the origin of hyperamylasaemia[43].

In chronic pancreatitis serum amylase concentration is usually normal during the quiescent phase[104]. An increase in both serum and urinary amylase is often seen during exacerbations, but as chronic damage progresses and pancreatic insufficiency develops, amylase elevation tends to become less pronounced and may often be in the normal range[36,104].

Table 2 *Drugs associated with hyperamylasemia related to acute pancreatitis*

Drugs	References
Opiates	(94)
Narcotic analgesics	(7, 94)
Cholinergic substances	(7, 94)
Azathioprine	(95)
Chlortalidone	(96)
Tetracycline	(97)
Thiazide diuretics	(7, 94)
Furosemide – Ethacrynic acid	(18, 94)
Aminosalicylic acid	(98)
Indomethacin	(99)
Oestrogens and corticosteroids	(7, 100)

Amylase and prognosis of acute pancreatitis

It is commonly accepted that the level of serum amylase bears no correlation with prognosis[3,12,17,105], although it has been proposed that the level of amylasaemia could be inversely related to the severity of the disease[36,48,106]. In the experience of Albo *et al.* for instance[48], one-third of their very ill patients with haemorrhagic pancreatitis had normal serum amylase levels. Rapid destruction of acinar tissue may be associated with low amylase levels[105]. This can explain the absence of hyperamylasaemia in some cases of severe acute pancreatitis[17,106]. One of us recently showed that the severity of the disease did not appear to differ significantly in terms of Ranson's score, CT findings and clinical course when comparing patients with acute pancreatitis who had normal or elevated amylasaemia[17]. Indeed, there was even a tendency for normoamylasaemic attacks to follow a milder course.

Neither the maximal value of amylase recorded within the first 48 h following admission and during the entire hospital course, nor the variability of serum amylase, have any prognostic value regarding the evolution of acute pancreatitis[17,105]. However, persistent hyperamylasaemia, although controversial[55], is currently considered to be a good indicator of the severity of the disease[3,107]. A serum amylase level which does not return to normal levels within 5–10 days should alert the clinician to possible complications such as pseudocysts, persistent phlegmon and abscess. Ultrasonography or CT scan are indicated in such cases, also allowing a guided-needle puncture and aspiration for bacteriological study or therapeutic drainage[4].

Lipase

Lipase, an enzyme that catalyses the hydrolysis of triglycerides into diglycerides and fatty acids, does not originate exclusively from the pancreas as first believed, but also emanates from other tissues such as the liver and the stomach[71,108]. However, lipase has recently been found, with elastase-1, to represent one of the most specific enzymes in diagnosing acute pancreatitis, the value for specificity approaching 90 per cent[109]. Lipase is completely reabsorbed after glomerular filtration and is not present in the urine, although in cases of tubular dysfunction significant lipasuria has been detected[110]. Pancreatic lipase is synthesized in the exocrine acinar cells and has a molecular mass comparable with amylase; similarly it is secreted directly in its active form into the pancreatic duct as opposed to other proteases and phospholipase A which are secreted as inactive proenzymes and activated once in the intestinal lumen. In acute pancreatitis, serum lipase appears complementary to amylase, since: (1) it rises more than amylase in case of alcoholic pancreatitis compared with biliary pancreatitis[111]; (2) it remains elevated for a longer period often extending beyond 2 weeks[3,53,107,111,112]; and (3) recently, one of our studies found that about two-thirds of cases of documented acute pancreatitis without increase of serum amylase could be identified by an elevated serum lipase level[17]. Others have also emphasized the usefulness of the combination of amylase and lipase determinations[3,112]. Despite these advantages, only a few studies have used serum lipase as a diagnostic marker of acute pancreatitis[4,17,113]. This reluctance to use lipase determination could be due to the method employed for serum level determination that is turbidimetric or nephelometric assays which are not available routinely in many laboratories[3,108]. However, recently introduced rapid methods such as the lipase latex agglutination test have been shown to be very accurate and require no more than 5 min to perform[114,115]. Moller-Petersen *et al.* carried out this rapid test on 417 patients with acute abdominal pain and found only six false positive and no false negative results in the whole series[116]. This test thus appears to be very promising in unmasking normoamylasaemic pancreatitis, especially in an emergency setting. Furthermore, the systematic addition of colipase to the assay, as recommended by some authors[117], will probably enhance the accuracy of the test.

Trypsin

The pancreatic proteases (trypsin, chymotrypsin, elastase, carboxypeptidases A and B) and phospholipase A are stored in the acinar cell and are secreted as proenzymes that have a negligible catalytic activity[118–120]. Trypsin is the key enzyme for rapid activation of all these proenzymes, including its own proenzyme, trypsinogen. Natural safeguards such as pancreatic trypsin inhibitor and blood antiproteases prevent trypsin activation within the pancreatic tissue and the pancreatic juice in the ductal system until it reaches the duodenum. There, the proteolytic enzyme cascade is triggered by enterokinase[121,122].

In human subjects, trypsin and trypsinogen have been for a long time considered to be exclusively present in the pancreas, since the enzyme was undetectable after pancreatectomy[119,123]. In these conditions, serum level determination of the enzyme was thought to fulfil ideally the criterion of organ specificity[124,125]. However, trypsin has been identified by immunofluorescence in the basal cells of the crypts in the small intestinal mucosa (Paneth cells), indicating the presence of an extrapancreatic source of these proteins and a similarity between the Paneth and pancreatic acinar cells[126].

Unfortunately, trypsin in the plasma was, for a long time, not accessible to enzymatic determination since the free form is complexed to antiproteases such as α-1-proteinase inhibitor and α-2-macroglobulin (α_2M) or is present as an inactive precursor, namely trypsinogen This limitation has been overcome by the development of a radioimmunoassay specific to human trypsin[124], measuring the enzyme, its zymogen and the trypsin bound to α-1-proteinase inhibitor, but the method does not allow the differentiation of one from the other. The technique also underestimates the plasma trypsin bound to α_2M, which has less than 15 per cent immunopotency[124]. The normal serum concentration of immunoreactive-trypsin (IRT) has been reported to be anywhere between 20 μg/ml and 400 μg/ml, and this can be elevated by as much as 40 times in acute pancreatitis with a similar amount appearing in the peritoneal exudate[125,127–130]. Low levels of IRT have even been detected in cases of chronic pancreatitis, pancreatic cancer, cystic fibrosis and diabetes mellitus. Indeed increased IRT has a specificity for acute pancreatitis which is probably above 90 per cent; false positive results have been found in cases of pancreatic cancer, choledocholithiasis, chronic renal failure and following ERCP[119,120,124,125,127]. IRT remains elevated longer than amylase and is in the same time range as lipase[109,115,129] For most authors IRT does not correlate with the severity of the disease[125,128,129]; after ERCP for instance, IRT increased irrespective of pancreatic injury[127]. On the other hand, some investigators have described correlations with severity[130]; this was the case, for example, when both IRT and p3-isoamylase remained elevated[55]. Like lipase, IRT could prove useful in unmasking normoamylasaemic acute pancreatitis, but time is the major factor limiting the clinical use of trypsin, its determination by conventional radioimmunoassay takes at least 24 hours[3,51,112,114]. Recent commercially available IRT kits have been proposed which require less than 6 h to complete the assay, but they need further evaluation.

Elastase-1

Elastase-1 is also a proteolytic enzyme with specific elastolytic action and an ability to hydrolyse haemoglobin, casein, fibrin and albumin[131]. Its role in inducing major vascular lesions in acute pancreatitis was well described in 1968[132]. Until the recent development of radioimmunological methods, investigations of circulating levels of the elastase-1 have been hampered by binding with circulating inhibitors[133,134] The immunochemically detected elastase-1 in plasma corresponds to elastase-1 and α-1-proteinase inhibitor complex, since there is no free circulating elastase and the elastase-1–α_2M complex has less than 2 per cent immunoreactivity[134]. High levels of elastase-1 have been described in all cases of acute pancreatitis, in up to two-thirds of pancreatic cancer, and less frequently in chronic pancreatitis[109,133,134]. Most studies do not demonstrate any significant advantages of this enzyme when compared with amylase, lipase, and IRT in the diagnosis of acute pancreatitis, and elastase-1 levels do not allow distinction between oedematous and necrotic forms[109,112,133,135], or between alcoholic and gallstone pancreatitis[109]. The main interest in elastase-1 determination in acute pancreatitis resides in the duration and the extent of elevation of the enzyme, which were significantly greater than those of amylase, lipase and trypsin[109,112,135]. Recently, Ventrucci *et al.*[109] noted that elastase-1 was the only enzyme still elevated on the seventh day in all patients with acute pancreatitis; the mechanism of this persistent elevation is still unclear. Furthermore, elastase-1 levels seem to be less affected than other proteases by renal insufficiency[136]. Thus, considering the longer half-life of plasma elastase, this enzyme could be of value as a late marker of pancreatic injury. However, like trypsin, the clinical implication of persistent elastase-1 elevation has not yet been established.

α_2-Macroglobulin (α_2M)

α_2M, α-1-proteinase inhibitor (also known as α-1-antitrypsin) and α-2-antichymotrypsin represent, quantitatively, the most important plasma antiproteases in man[137–139]. Their main function consists in preventing the existence of free proteolytic enzymes such as trypsin and elastase[119,120,129,137–139]. α_2M is a high weight glycoprotein of about 800 000 Da present in human plasma in high concentration (about 2 mg/ml), representing most probably the key antiprotease[137–139]. After an initial limited proteolysis, α_2M undergoes a drastic change in its spatial configuration enabling it to 'entrap' and inactivate a wide variety of circulating proteases. Nevertheless, interestingly, the proteolytic activity of α_2M-protease complex towards low molecular weight substrates is not completely inhibited as is the case with parathormone, vasopressin, angiotensin, and proinsulin[137–139]; these complexes may have a role in the continuation of proteolytic activity in acute pancreatitis[120,129]. The clearance of the α_2M-protease complex is achieved by cells of the reticuloendothelial system, hepatocytes, adipocytes and fibroblasts through specific cellular receptors recognizing this complex[137–139]. However, the respective importance of these 'scavenger cells' remains unknown[137–139]. In acute pancreatitis, the site of complex formation has not been established yet[120,129]. Free α_2M has a half-life of about 100 h but is cleared within 10 min by the scavenger cells once bound to proteases[120,129].

The decreased level of α_2M has been found to be related to the severity of the clinical course of acute pancreatitis[120,125,129]. In contrast, α-1-proteinase inhibitor and α-2-antichymotrypsin levels rise along with those of C-reactive protein, since these antiproteases probably also belong to the group of acute phase proteins[129]. Furthermore, although the level of α_2M at admission hardly differs between severe and mild attacks, it seems to decrease more profoundly in the patients with severe acute pancreatitis becoming significantly depressed by 5 days after hospitalization[120,125,129]. The sensitivity of α_2M for the identification of pancreatic necrosis has recently been estimated as being close to 85 per cent; necrosis being confirmed histologically or by CT findings[135]. α_2M level does not seem to be influenced by sepsis, but low values have been reported in the case of major burns, multiple myeloma and therapy with fibrinolytic agents[140], As in acute pancreatitis, the main mechanism of the decrease of α_2M in all of these conditions seems to be a consumptive plasma depletion following protease release and clearance of formed complexes by the reticuloendothelial system.

Although a relation between the decrease of plasma α_2M and the severity of acute pancreatitis is logically conceivable, the true clinical implication is still unclear. Supplementation of plasma antiproteases with fresh frozen plasma has been suggested as therapeutic[141], but the efficacy of this treatment remains unproven[142].

Phospholipase A_2

The presence at autopsy of significant amounts of lysolecithin in necrotic tissue in fatal cases of acute pancreatitis has suggested a central role for phospholipase A_2 in the pathogenesis of the disease[143,144]. This enzyme is known to convert lecithin and cephalin in cell membranes and bile to their toxic lysocompounds[144,145], and probably also splits the alveolar phospholipids leading to the respiratory distress syndrome seen in some cases of severe acute pancreatitis[145]. The importance of phospholipase A_2 in acute pancreatitis is now supported by both experimental and clinical studies[143,144]. Phospholipase A_2 is activated by trypsin, but the latter paradoxically abolishes its activity by cleaving a bond in the amino acids of the active site on the molecule. It is probable that successive cycles of activation and inactivation in an appropriate environment in the pancreas could lead to the coagulation necrosis that is attributed to uncontrolled activity of phospholipase A_2[144]. In contrast to protease, there is no known endogenous inhibitor of phospholipase A_2. On the other hand, animal models of phospholipase A_2-induced acute pancreatitis have shown that the intraductal infusion of enzyme alone causes only mild acinar necrosis, and nearly all zymogen granules are preserved, whereas bile salts and phospholipase A_2 in combination cause extensive pancreatic necrosis, suggesting that membrane dissolution precedes hydrolysis of the constituent phospholipids[143,144]. In man, immunoreactive serum phospholipase A_2 may be elevated by as much as 500-times in acute pancreatitis, and has been found to have prognostic value[144–146], correlating especially well with pulmonary complications[145]. However, it is still unclear how much of the enzyme is of pancreatic origin[144–146]. As at least two immunologically distinct phospholipases A_2 exist in the plasma of patients with acute pancreatitis, future results should therefore be interpreted with caution[147]. Assay procedures are very difficult and time-consuming and are not yet available on a routine basis.

Ribonuclease (RNAase)

Numerous types of RNAase exist. They can be differentiated from one another by the pH of optimal activity[148]. Ten years ago, Warshaw and Lee[149], in a small series, reported that an acid RNAase of low molecular weight – resulting from the release of cell breakdown in anoxic pancreas – was an indicator of pancreatic necrosis. These authors found that 11 of 13 patients with elevated RNAase had pancreatic necrosis; and of the patients with pancreatic necrosis only one did not have an elevation of serum RNAase. However, the value of RNAase determinations is controversial. Some authors considered an early increase of the enzyme to be pathognomonic of severe acute pancreatitis[150], while others found no correlation between the clinical course and enzyme levels[151]. A rise in RNAase levels is not specific for acute pancreatitis since different clinical conditions are associated with elevations of this enzyme, namely pancreatic cancer, leukaemia, major burns, trauma, and renal failure[152]. Further investigations are needed before serial determination of RNAase can be recommended as a test for the selection of patients who will benefit from early debridement[3].

Carboxypeptidase

The digestive actions of carboxypeptidases have been widely studied, but few reports have emphasized the variation of serum levels of the enzyme in acute pancreatitis. In 1974, Fujii *et al.* reported a low activity of carboxypeptidase A in pancreatic cancer, acute and chronic pancreatitis and liver cirrhosis[153]. In acute pancreatitis, with the use of fluorimetric detection, this enzyme and its precursor were found to be more specific to the pancreas than amylase and lipase[154]. Recently, a more convenient colorimetric assay for carboxypeptidase A has been described[155]. Radioimmunoassay with antibodies specific to carboxypeptidase B has enabled detection of the active enzyme in the serum of patients with acute pancreatitis and has shown that its presence is proportional to the amount of active trypsin bound to plasma inhibitors. Thus, theoretically, carboxypeptidase B offers information on circulating levels of active pancreatic proteases, and hence on pancreatic injury[156].

Carboxylic ester hydrolase

Earlier assays were not specific enough to differentiate the two pancreatic lipolytic triglyceride hydrolysing enzymes, colipase-dependent lipase and carboxylic ester hydrolase[157]. The use of enzyme-linked immunosorbent assay (ELISA) has facilitated this distinction Carboxylic ester hydrolase, also known as cholesterol esterase, is a non-specific lipase; it hydrolyses cholesterol esters, fat-soluble vitamin esters and triglycerides[157,158]. This enzyme is also elevated in lactating mammary glands and some mammary tumours[158]. The superiority of the enzyme over current amylase or lipase determinations in the diagnosis of acute pancreatitis, as recently suggested[158], requires further investigations.

C-reactive protein

C-reactive protein is a non-specific but sensitive protein indicating tissue injury, inflammatory response, bacterial infection and ischaemic conditions[159]. It has no value in establishing the diagnosis of acute pancreatitis but may be a very sensitive indicator of pancreatic injury and useful for the follow-up of patients[135,160]. An elevation above 100 mg/l has been reported to detect 95 per cent of cases of pancreatic necrosis compared with 85 per cent for CT findings and 38 per cent for ultrasonography[135].

Methaemalbumin

Methaemalbumin results from intravascular haemolysis and is a combination of a breakdown product of haemoglobin with albumin which appears 72 h or more after the onset of acute pancreatitis[161]. The significance of methaemalbumin in the blood is controversial and its correlation with the severity of the disease[162] has not been substantiated[1,3].

Fibrinogen

Coagulation abnormalities are frequent in acute pancreatitis and can lead to severe disseminated intravascular coagulopathy. Release of trypsin as well as imbalances of proteases–antiproteases complexes have been incriminated[163] Correlations have been established between the severity of acute pancreatitis and the level of coagulation factors such as fibrinogen[163–165]. Berry *et al.*[165] suggested that a fibrinogen level greater than 6·0 g/l is a reliable predictor of future complications and equivalent to standard multifactorial prognostic tables, but this observation was not confirmed by other investigators[166].

Other laboratory tests for the future

Oxygen-derived free radicals play an important role in many diseases, especially in ischaemic disorders, causing injury to capillary endothelial cells; their role in the pathogenesis of acute pancreatitis has recently been promoted[167]. The estimation of the concentration or reactivity of these free radicals still belongs to the field of specialized laboratories.

In man, enterokinase is an enzyme strictly localized in the brush border of the enterocyte lining the duodenum and upper jejunum. The catalytically activated enterokinase could be a key triggering factor in acute pancreatitis due to pancreatico-biliary reflux[168]. Measurement of the enzyme in blood, in bile or in ascitic fluid in cases of acute pancreatitis has been suggested for future investigation. We personally doubt the potential fruitfulness of this line of enquiry because, if enterokinase is involved (and this is certainly unproven) its site of action is more likely to be intraductal rather than systemic.

Activation of trypsinogen by enterokinase in the lumen of the proximal small intestine during digestion liberates a sequence of peptides at the amino terminus of the molecule known as trypsinogen activation peptides (TAP)[169]. In physiological conditions, TAPs are probably degraded in the intestinal mucosa by proteases and oligopeptidases In the case of severe acute pancreatitis, it has been suggested that TAPs could exist within the pancreas and inappropriate release into the blood and peritoneal cavity can occur New radioimmunoassay techniques have enabled the detection of free plasma TAPs offering the means for further investigation concerning an eventual correlation between plasma level of this peptide and the severity of acute pancreatitis

The complement system undoubtedly plays a role in acute pancreatitis. The C5-peptide for instance, has been implicated as an important mediator of acute lung injury, and furthermore, it was found in the serum of patients with acute pancreatitis[170]. Plasma levels of this peptide may correlate with pulmonary complications[170].

Discussion

The major difficulty in the evaluation of acute pancreatitis through serum markers is the lack of a reliable objective diagnostic method. Acute pancreatitis can vary in its severity from a very mild disease already resolved at admission to a devastating form involving all systems and leading to death within hours. Acute pancreatitis can present as a single episode or as a series of recurrences. Efforts to create a satisfactory international classification have encountered many difficulties; it often remains unclear, for example, whether the recurrent forms should be classified under recurrent acute pancreatitis or relapse of chronic pancreatitis; this distinction has even been removed from recent classifications[171,172]. This lack of a universal definition of acute pancreatitis largely explains the discrepancies concerning the relative diagnostic value of laboratory tests and the resulting confusing opinions regarding their respective sensitivity and specificity. Another source of confusion resides in the methodology of the enzymatic level determinations and especially the variability and absence of standardization of chemical substrates used in different centres. Such laboratory subtleties can easily escape the clinician's attention, and lead to erroneous conclusions about the diagnostic efficiency of an enzyme.

Given the absence of any specific clinical signs, acute pancreatitis should be part of the differential diagnosis established for any patient admitted with abdominal pain, especially since atypical presentation is not uncommon. Systematic measurement of serum amylase, lipase or other enzymes in all cases of abdominal pain is difficult to justify, but a screening test using a urinary amylase strip (e g the Rapignost test) could be useful. This method is quite sensitive and represents an acceptable alternative to serum determinations and could alert the clinician to the possibility of acute pancreatitis. Nevertheless, as false positive and false negative results exist[76,77], complementary serum enzyme determinations are mandatory either if the test is positive or if there are clinical arguments in favour of acute pancreatitis. Total serum amylase, in spite of its sensitivity of approximately 80 per cent[17] and 70 per cent specificity[19,20], remains the most convenient laboratory test for the diagnosis of acute pancreatitis because of the simplicity and rapidity of its determination. In our opinion, the systematic association of serum amylase with serum lipase determination will eliminate most false negative and false positive results. We think that isoamylase determinations will not significantly enhance the accuracy of the combination amylase–lipase, although they could be helpful in situations of hyperamylasaemia associated with normolipasaemia. The calculation of Cam:Ccr ratio is useful only in special conditions such as hyperlipidaemic serum, macroamylasaemia and renal insufficiency.

Of the enzymatic systems other than amylase and lipase, the proleolytic enzymes deserve comment, although their diagnostic use is controversial. These enzymes are synthesized as proenzymes in zymogen granules and are activated only when secreted into the digestive tract. Pathological activation and interactions with circulating antiproteases undoubtedly play a role in the genesis of pancreatic injury. However, the exact mechanism is unclear. Progress in enzyme determination methodology is still needed in order to understand fully their role. Although their serum level determinations are not routine laboratory tests and while their assays are considerably time consuming (as opposed to those of amylase and lipase), some of these proteases seem very promising as late markers of the evolution of acute pancreatitis and may provide a valuable non-invasive assessment of the severity of the disease. For instance, IRT and elastase-1 determinations may be indicated as complementary diagnostic markers in rare cases of normoamylasaemic and normolipasaemic acute pancreatitis, especially when the delay between the onset of the symptoms and time of admission does not allow the exclusion of a return to normal values of the usual enzymatic markers. Nevertheless, we believe that in such situations the CT scan still represents a more accurate diagnostic tool[17].

The role of RNAase, phospholipase A_2, α_2M and C-reactive protein as indicators of the severity of the disease should be further investigated. With the development of simpler laboratory methods they could represent an interesting alternative to standard prognostic tables, which commonly require numerous measurements over a 48 h period[173,174]. In our opinion, these markers will allow the selection of patients who would benefit from complementary and serial CT scans and, finally, identify those requiring surgery.

Diagnostic peritoneal lavage has been advocated as a manoeuvre early in the course of acute pancreatitis. Studies of enzymes in the peritoneal fluid in acute pancreatitis have failed so far to yield convincing results, but represent an interesting alternative which certainly deserves further investigation.

Finally, we should keep in mind that in pancreatitis of alcohol origin, the peak level of most pancreatic markers is diminished due to tissue damage resulting in a reduced production capacity of the organ. Therefore, the sensitivity of laboratory tests in detecting alcohol-induced pancreatitis may remain deceptive in comparison with gallstone pancreatitis.

In conclusion, serum measurements of total amylase coupled to lipase represent to date the most practical and accurate laboratory method for diagnosing acute pancreatitis. In our opinion, other enzymatic determinations, although now often proposed in new commercial kits, should still be subject to controlled studies and systematically evaluated in terms of clinicobiochemical criteria, CT-scan findings and clinical course.

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Late complications of pancreatic trauma

Pancreatic trauma is rare and experience concerning its management is consequently limited. Lessons learnt in the investigation and treatment of a group of 11 patients (median age 28·0 years, range 14–44 years), who presented with the sequelae of trauma, are described. These patients were referred to a centre with an interest in pancreatic disease at a median time of 6·0 months (range 1·5–34 months) after blunt (n = *9*) *or penetrating* (n = *2*) *injury to the pancreas. Ten of the 11 patients had undergone either single* (n = *4*) *or multiple* (n = *6*) *previous operations. Ten of the 11 patients had either strictures or disruptions of the main pancreatic duct demonstrated by endoscopic retrograde cholangiopancreatography (ERCP) and ultrasonography* (n = *8*) *or by exploration of the pancreas* (n = *2*)*. Satisfactory results were achieved by non-operative treatment in one patient and by distal pancreatectomy in eight. One further patient, who underwent distal pancreatectomy, later required completion resection because of unsuspected ductal injury in the head of the gland. The final patient continued with symptoms of pancreatitis after pancreaticoduodenectomy. It is concluded that the non-resolving sequelae of pancreatic trauma are associated with injury to the main pancreatic duct and that specialist investigation should be performed before surgical intervention is contemplated.*

Keywords: Pancreatic trauma, main pancreatic duct, endoscopic retrograde cholangiopancreatography

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Pancreatic trauma is uncommon and is reported to occur in only 3–12 per cent of abdominal injuries[1]. In a recent study, Nilsson *et al.*[2] estimated that the annual incidence of pancreatic injury was 0·4 cases per 100 000 of the population examined and hence it is unusual for any individual surgeon to gain extensive experience in the management of this condition. The initial mortality rate associated with pancreatic injury remains high, up to 20 per cent in some series[3], but death is usually due to concurrent major vascular or visceral injury rather than to pancreatic trauma itself. Up to 30 per cent of survivors may develop pancreatic complications such as pseudocyst, abscess and fistula, all of which can present months or years after injury and provide considerable problems in management[4,5].

This surgical unit is a major centre for the management of pancreaticobiliary disease and deals with 50 new cases of benign pancreatic disease per annum. Over a 15-year period 11 patients have been referred with persistent symptoms following blunt or penetrating pancreatic injury. The present study reviews their previous surgical management, the types of complications and the further investigation and treatment of these patients.

Patients and methods

The case notes were reviewed of 11 patients who were referred between January 1973 and March 1988 to the Middlesex Hospital with late problems after pancreatic trauma. Particular attention was directed to the nature of any previous surgery, the types of complications at referral and the anatomy of the main pancreatic duct.

Results

There were seven male and four female patients with a median age of 28·0 years (range 14–44 years). Nine patients had originally suffered from blunt abdominal trauma and two had sustained penetrating injuries. The median time interval between the original injury and referral to The Middlesex Hospital was 6·0 months (range 1·5–34 months).

Previous surgical management

Ten of the 11 patients had undergone abdominal exploration after injury. Eight had been explored within 48 h but two others had not been explored until 2 and 3 months respectively after injury. In those eight patients who had undergone early exploration, the laparotomy findings which indicated pancreatic injury included retroperitoneal haematoma or mass in four patients, capsular tears and disruption of the pancreatic parenchyma in the two patients with penetrating trauma, and bile stained effusion with fat necrosis in one patient. The final patient had no findings suggestive of pancreatic injury. Pseudocyst was the only indication of previous pancreatic injury in those two patients who had been operated on at 2 and 3 months after injury. Associated findings included ruptured spleen (two cases), lacerated mesentery or mesocolon (two cases), fractured vertebrae (two cases), lacerated liver (one case), duodenal injury (one case) and fractured ribs (one case). Of those eight patients who were explored within 48 h of injury, five had undergone laparotomy with external abdominal drainage and three had undergone laparotomy without drainage. The two patients who underwent surgery at 2 and 3 months after injury had had cystgastrostomies performed.

Early reoperations for the development of intra-abdominal sepsis, pancreatic fistula or pseudocyst had been undertaken in six of the ten patients. Of these, four patients had had two operations, one had had three operations and one patient had undergone four operations. These procedures took the form of further external abdominal drainage only (four cases) or cystgastrostomies (two cases).

Complications at referral

Pancreatic pseudocyst was the main indication for referral in five patients and three of these had undergone previous cystgastrostomies. The other indications included recurrent acute pancreatitis with intermittent hyperamylasaemia in four patients, pancreatic fistula in one patient and pancreatic abscess in another.

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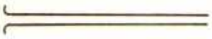
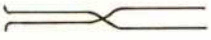
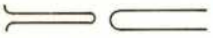
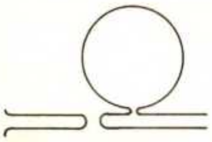
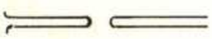
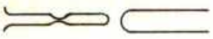
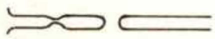
Table 1 *Ductal status in 11 patients with late complications of pancreatic trauma*

Anatomy	Ductal status	Mode of presentation
	Normal	Recurrent pancreatitis (1)
	Stricture with upstream dilatation	Fistula (1), recurrent pancreatitis (1)
	Disruption with upstream dilatation	Pseudocyst (2)
	Disruption with distal end communicating with pseudocyst	Pseudocyst (1)
	Disruption only	*Pseudocyst (2), abscess (1)
	Stricture and disruption with upstream dilatation	Recurrent pancreatitis (1)
	Stricture and disruption only	*Recurrent pancreatitis (1)

The number of affected patients are given in parentheses; * includes 2 patients who were assessed at pancreatic exploration

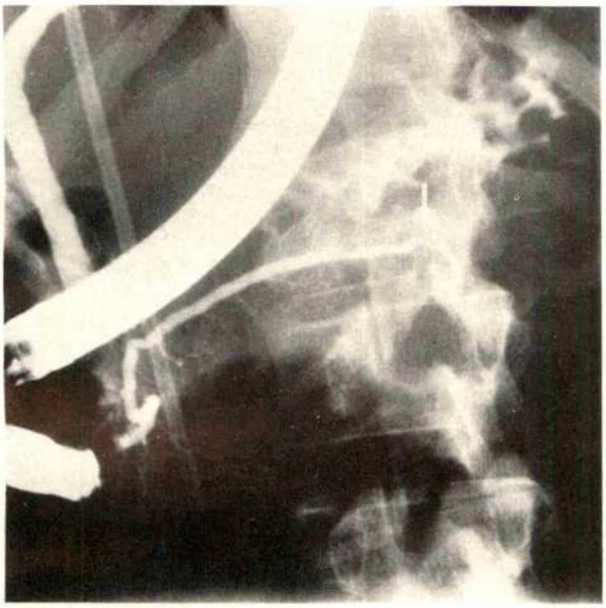


Figure 1 *Endoscopic retrograde cholangiopancreatography showing complete obstruction (arrow) of the main pancreatic duct at the junction of the body and tail of the gland*

Modes of investigation and ductal status

Nine of the 11 patients were investigated using a combination of ultrasound scanning and endoscope retrograde cholangiopancreatography (ERCP) and two of these patients also had computed tomographic (CT) scans. The two other patients, who presented in the early part of the series, did not undergo any preoperative imaging, the integrity of the main pancreatic duct being assessed at pancreatic exploration.

Ten of the 11 patients had either strictures and/or disruption of the main pancreatic duct (*Table 1*). Eight patients had injury to one region of the main duct only but two others had more than one area involved (*Table 1*). The ductal lesions were situated in the body of the pancreas (four patients), the neck (two patients), the junction of the body and tail (one patient; *Figure 1*), the junction of neck and body (one patient), the head and body (one patient) and the head and neck (one patient: *Figure 2*).

Further management

One patient with a ductal stricture in the neck of the gland and a fistula from a first order duct was treated conservatively. The fistula closed after 5 weeks of total parenteral nutrition. The remaining ten patients were managed surgically. Nine patients, eight of whom had duct injury in the neck of the gland or beyond, had a distal pancreatectomy. The ninth patient had a normal pancreatic duct but surgery was undertaken because of persistent pain and a suspected pseudocyst in the tail of the pancreas. The remaining patient who had a ductal stricture and disruption in the head and neck of the pancreas had a pancreaticoduodenectomy.

Outcome

Two patients were not followed up. One of these underwent distal pancreatectomy at the referring hospital and the other returned to her home country 1 month after operation at the Middlesex Hospital.

For the remaining nine patients the duration of follow up ranged from 2 months to 7 years. Patients were assessed for the presence or absence of abdominal pain and any change in bowel activity. Regular estimations of blood glucose level were also undertaken. The patient who underwent pancreaticoduodenectomy continued to experience pain and developed pancreatic exocrine failure. She had been referred 6 months after injury with recurrent acute pancreatitis due to stricture and disruption of the proximal pancreatic duct. The origin of her postoperative pain was thought to be chronic pancreatitis in the residual gland. One other patient, who initially underwent distal pancreatectomy, later required completion duodenum preserving pancreatectomy because of unsuspected ductal stricture in the head of the gland which produced further pancreatitis, local sepsis and stricture of the distal common bile duct. This patient was one of the two who did not undergo preoperative ERCP, ultrasound or CT scanning. Of the

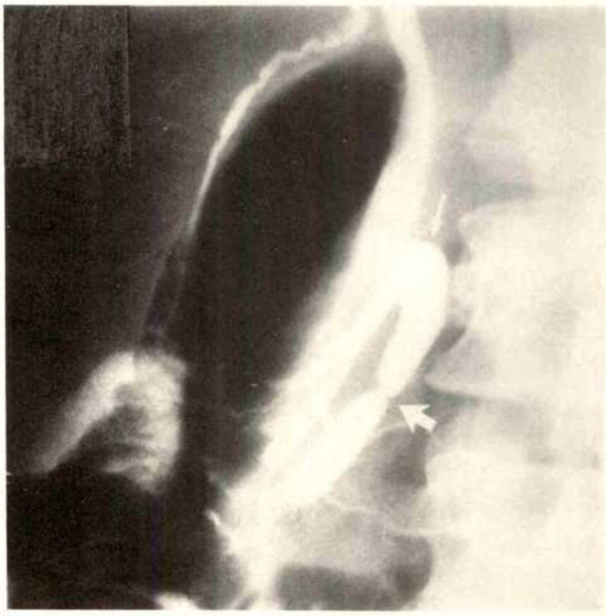


Figure 2 *Endoscopic retrograde cholangiopancreatography showing a stricture (thick arrow) and complete obstruction (thin arrow) of the main duct in the head and neck of the pancreas*

remaining seven patients, one has developed pancreatic exocrine insufficiency but there have been no instances of endocrine failure. Eight of the nine patients are pain free.

Discussion

The findings from the present study are in keeping with those of several authors who have emphasized that the operative assessment of pancreatic injury can be difficult and that significant injuries may be easily overlooked at the time of laparotomy for abdominal trauma[4–6]. Heitch *et al.*[3] and others[7] have described criteria, based on the appearance of the pancreas at operation, for assessing the severity of pancreatic injury. However, such assessment is not always reliable. The retroperitoneum may be too traumatized and obscured by haematoma to permit the detection of pancreatic capsular tears or main duct disruptions, and transections of the pancreas may be concealed beneath an intact capsule[8]. Certain authors have stressed that the identification of main pancreatic duct disruption is particularly important because such injury is associated with a high degree of postoperative morbidity unless distal pancreatic resection is performed[9–11]. This was confirmed in the present series of patients but whether extensive dissection to determine the state of the pancreatic duct should be done at the original operation is open to debate.

The contention that complications which occur months or years after pancreatic trauma can be explained on the basis of undetected duct disruption is supported by the results of specialist investigation in the present study. Pseudocysts, abscesses and fistulae are well documented sequelae of pancreatic trauma and are presumably the result of continued leakage of pancreatic enzymes from a disrupted ductal system which has failed to heal following injury[4,8]. By contrast, recurrent acute pancreatitis due to ductal stricture is less well recognized but it occurred in three of our patients. It seems likely that incomplete duct transection may subsequently heal by fibrosis with stricture formation.

Although the classical site of pancreatic duct injury lies over the vertebral column[4,12], it is clear from this series that disruptions of the duct can occur in any of the anatomical subdivisions of the gland. It has been noted that more than one region may be involved[9] and our data support this observation. As demonstrated by one patient in the present study, these findings carry important practical implications because strictures or disruptions may remain undetected unless imaging is undertaken before definitive surgery.

Accurate diagnosis of main duct disruption soon after injury would be of value in the prevention of the delayed sequelae of pancreatic trauma described in this and other studies[4,9,13]. Sugawa and Lucas[14] have recently drawn attention to the role of ERCP in the early evaluation of pancreatic trauma and Barkin *et al.*[15] correctly identified duct disruptions in four of 14 patients with suspected pancreatic trauma who underwent ERCP within 72 h of injury. ERCP represents a major advance in the assessment of the injured pancreas. In patients with suspected pancreatic trauma, who do not require immediate operation for concommitant life threatening injury, ERCP should be undertaken to define the nature of the trauma more clearly.

On the other hand, in those patients who do require immediate surgery after abdominal trauma and in whom main pancreatic disruption is suspected but not confirmed following gentle exploration of the pancreas, we support the opinion of Hendel and Rusnak[9] that careful external drainage provides an acceptable and preferable alternative to blind pancreatic resection. In the event of pancreatic complications, specialist assessment of the pancreas by a combination of ultrasound, CT scanning and ERCP should be undertaken to determine the extent of the disease and the status of the duct. In this way a sensible definitive procedure can be planned to minimize the risk of further complications or late recurrence of pancreatic disease.

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Intravenous digital subtraction angiography for extracranial carotid artery disease

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Intravenous digital subtraction angiography is relatively hazardous and inaccurate. It appears from the literature to have little place in either the screening of patients with putative carotid artery disease or in the assessment of those about to undergo carotid endarterectomy.

Keywords: Digital subtraction angiography, extracranial carotid artery disease

Radiologists perform angiograms but the decision to do an angiogram generally rests with the surgeon and a knowledge of the benefits and drawbacks of angiography is, therefore, of considerable importance in surgical practice. Such knowledge is especially relevant in the field of extracranial cerebrovascular disease for which angiography has well recognized hazards and for which other techniques, notably ultrasonography, compete for the position of most useful investigative technique. Although the place of carotid endarterectomy remains to be defined completely[1,2], it is widely advocated for patients with carotid territory transient ischaemic attacks due to extracranial carotid artery disease. The operation is usually preceded by angiography to demonstrate the site and morphology of the stenosis to be removed[3], and it has been suggested that when perioperative stroke occurs in less than 3 per cent of patients, stroke incidence may be reduced in the long term, compared with the natural history of the untreated disease[1,2,4]. However, conventional angiography of the carotid artery may itself provoke a major stroke in as many as 2·4 per cent of patients[5] and it is principally this risk which has prompted the search for safer techniques of diagnosing extracranial carotid artery disease.

One such technique is intravenous digital subtraction angiography (IVDSA)[6–10], and early reports suggested that in many instances IVDSA might replace conventional angiography[11–15], especially in terms of screening patients for carotid artery disease[16,17]. This early promise seems not to have been realized[18,19] and, indeed, it has become clear that the complications of the technique may pose a greater problem than was initially anticipated[20]. Furthermore, major concern has been voiced in some quarters over the difficulty in obtaining images on a regular basis that are of comparable quality to those obtained with conventional angiography, and the factors that limit image quality have been described[21]. Another problem, particularly when IVDSA is used for screening purposes, is that the negative predictive value of a normal IVDSA result is low[22], which implies that significant stenoses may be overlooked. With this background, we have examined the current value of IVDSA, as outlined in the literature, by assessing two features of the technique, namely risk and accuracy. To eliminate any bias inherent in retrospective analyses we have considered only prospective data. In addition, we have included reports of the use of IVDSA only in suspected extracranial carotid artery disease because of evidence suggesting that the risk of carotid angiography varies with different pathologies[23]. When considering the accuracy of IVDSA, we have assessed both its ability to measure the absolute degree of stenosis and its ability to differentiate between haemodynamically significant and haemodynamically insignificant lesions.

Definition of complications

Only two prospective studies are available which fully describe the complications of IVDSA[24,25]. The occurrence of two groups of complications was recognized, namely major systemic complications, such as myocardial infarction and pulmonary oedema, and neurological complications. The latter were subdivided into transient ischaemic attacks in which the neurological deficit resolved totally within 24 h of angiography, minor stroke (resolution within 7 days) and major stroke (resolution after 7 days or no resolution)[5].

Definition of accuracy

The accuracy of a particular patient's investigation was assessed by comparing the estimated degree of stenosis of the internal carotid artery on IVDSA with that on conventional angiography or with that obtained by direct measurement at endarterectomy. Based on the grading of stenosis of Chilcote *et al.*[26], who used categories from zero to 100 per cent in increments of 20 per cent, we considered that a given result using IVDSA was accurate when the grade of stenosis as judged by this method and conventional angiography was the same; any discrepancy was considered to represent an inaccurate study. This differs from the definition of 'accurate' used by Chilcote *et al.*[26] and Russell *et al.*[27] who regarded as accurate a result using IVDSA that was within one grade either side of the conventional angiographic grade. Such a definition obviously increases the apparent accuracy of IVDSA: for instance, it allows stenosis measurements of both 21 and 80 per cent to be regarded as in agreement with any conventional angiographic measurement between 41 and 60 per cent. Because 'agreement' could represent a difference of up to 39 per cent between the stenosis observed from IVDSA and from conventional angiography for any given patient using the grades of Chilcote *et al.*, we believe that our more stringent definition is more relevant to clinical practice. This alteration in definition accounts for the discrepancy between the accuracy of IVDSA reported by the original authors and the re-evaluated accuracy reported here.

The accuracy of IVDSA in any series was first of all taken as the ratio, expressed as a percentage, of the number of accurate studies (where both methods agreed) to the total number of arteries examined by both techniques. This is complicated by the fact that not all IVDSA examinations were technically adequate and that both the definition of an inadequate study and the details of such studies were described differently by different authors. Clearly, if inadequate studies are not considered, the apparent accuracy of IVDSA in a series rises. To allow for this we have considered, unless specific contrary information was presented, that 'uninterpretable', 'poor' or

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Table 1 *Numbers of complications of intravenous digital subtraction angiography*

Reference	Year	No. of patients	Transient ischaemic attack	Major stroke	Major systemic complication
Aaron *et al.*[24]	1984	102	2	1	23
Ball *et al.*[25]	1985	500	1	1	32
Total (%)		602 (100)	3 (0·5)	2 (0·3)	55 (9·1)

Values in parentheses are percentages

Table 2 *Overall accuracy of intravenous digital subtraction angiography*

Reference (year)	'Gold standard'	Adequate studies	Poor studies	Accurate and adequate studies	Accurate and poor studies	Accurate studies total	All studies total	Overall accuracy (%)
Chilcote *et al.*[26] (1981)	Conventional angiography	143	55	104	13	117	198	59
Russell *et al.*[27] (1983)	Conventional angiography	128	14	87	0	87	142	61
Wood *et al.*[28] (1983)	Conventional angiography	95	7*	55	0	55	102*	54
Reilly *et al.*[29] (1984)	Operative specimen	39	26	37	7	44	65	68
Mendel *et al.*[32] (1987)	Conventional angiography	11	3	7	0	7	14	50
Glover *et al.*[33] (1984)	Conventional angiography	56	6*	38	0	38	62*	61
Turnipseed *et al.*[34] (1982)	Conventional angiography	71	1	69	0	69	72	96
Total						417	655	64

* Derived value

'non-diagnostic' studies were for present purposes inaccurate. In one paper the absolute number of inadequate studies using IVDSA in the subgroup of patients also undergoing conventional angiography was not reported[28], but this could be estimated using the reported overall incidence (7 per cent) of unsatisfactory studies using IVDSA. We have, as a secondary consideration, also estimated the accuracy of 'adequate' studies by excluding the inadequate studies, although this estimation is less reliable because of author variation in the definition of a poor study.

The accuracy of IVDSA in determining the presence or absence of a lesion of haemodynamic significance was also estimated. This was hampered by variation in the boundaries of grades of stenosis described by various authors, so, depending on the series, a haemodynamically significant lesion has been taken variously as one of stenosis greater than 60, 70 or 75 per cent diameter. IVDSA was considered accurate in this respect if it agreed with conventional angiography on the presence or absence of a lesion of the appropriate 'haemodynamic' severity, according to the grading system of the relevant paper.

Complications

The result of the two studies which detail complications are shown in *Table 1*. In one study, IVDSA in 102 patients caused one major stroke, two transient ischaemic attacks and 23 major systemic complications, including one cardiac arrest and probably two myocardial infarctions. In the other study of 500 patients there was one major stroke, one transient ischaemic attack and 32 major systemic complications. These data suggest a 0·3 per cent risk of major stroke, a 0·5 per cent risk of transient ischaemic attack and a 9·1 per cent risk of major systemic complication for IVDSA when assessing extracranial carotid artery disease.

Accuracy

Four prospective studies comparing IVDSA with conventional angiography or the appropriate operative specimen were identified[26–29]. Chilcote *et al.*[26] included full details of all interpretable studies. Two studies which were uninterpretable because of power injector failure were not considered to be specifically failures of IVDSA and were excluded. The remaining uninterpretable studies were considered inaccurate for the purposes of the present analysis[26]. Russell *et al.*[27] also give full details of all interpretable studies. We considered their remaining uninterpretable studies to be inaccurate. Wood *et al.*[28] give full details of interpretable studies, but, as described above, the number of uninterpretable studies has been derived using their overall figure for uninterpretable IVDSA (7 per cent). Reilly *et al.*[29] used the relevant endarterectomy specimen as the standard against which IVDSA was assessed. They report the accuracy of IVDSA in patients with adequate and inadequate studies without using grades of stenosis, which means that their data cannot be used in assessing the accuracy of IVDSA with regard to lesions of haemodynamic significance.

Prospective data comparing IVDSA with conventional angiography also exist in studies comparing both IVDSA and ultrasonography with conventional angiography. Five such studies were identified[30–34], of which two were considered unsuitable for inclusion here. D'Alotto *et al.*[30] present their results in such a way that the data required by the present study are inaccessible, and Zweibel *et al.*[31] do not distinguish between details of internal carotid evaluation and those of external carotid studies. Although Mendel *et al.*[32] compared IVDSA with conventional angiography in only 14 vessels, they give full details. Glover *et al.*[33] also give full details of all vessels evaluated with both conventional angiography and a technically adequate IVDSA, although not of the number of

Table 3 *Accuracy of intravenous digital subtraction angiography related to haemodynamically significant lesions*

Author (year)	Significant lesion (%)	Accurately ascribed significant lesion	Accurately ascribed insignificant lesion	Total accurately ascribed lesions	Total all studies	Accuracy (%)
Chilcote *et al.*[26] (1981)	>60	41	125	166	198	84
Russell *et al.*[27] (1983)	>75	31	86	117	142	82
Wood *et al.*[28] (1983)	>60	28	61	89	102	87
Mendel *et al.*[32] (1987)	>60	4	5	9	14	64
Glover *et al.*[33] (1984)	>70	14	38	52	62	84
Turnipseed *et al.*[34] (1982)	>75	32	39	71	72	99
Total				504	590	85

inadequate studies using IVDSA. Their incidence of inadequate studies using IVDSA overall (10 per cent) is used to estimate the number of inadequate studies in patients who also had conventional angiography. Turnipseed *et al.*[34] present full details of all studies.

Table 2 shows data relating to the overall accuracy of IVDSA at determining internal carotid stenosis. The series combine to give an overall accuracy of 64 per cent. If only technically satisfactory examinations are included, the figure rises to 73 per cent. *Table 3* shows that the accuracy of IVDSA at detecting haemodynamically significant lesions is 85 per cent.

Discussion

Reviewing IVDSA in 1985, Sumner *et al.*[35] noted 'no strokes or serious neurological events' from the technique. In 1989 it is now clear, even from the limited number of prospective studies available to us, that IVDSA for extracranial carotid disease does carry some risk of stroke as well as a pronounced risk of major systemic complications. These systemic complications offset the benefit of a reduced stroke risk when IVDSA is compared with conventional angiography. Broadly speaking, the risk attached to IVDSA, although rather different in nature, is not appreciably less than that from conventional angiography. Even if the accuracy element is ignored, the problem of complications alone should rule out IVDSA as a screening procedure for patients with putative extracranial carotid artery disease. When the apparent accuracy is also considered, the technique in most centres seems to be unequal to the task of usefully delineating disease in the carotid artery before carotid endarterectomy.

The attraction of IVDSA for screening purposes becomes even less when one considers the relative success of ultrasonography, a safe and much less expensive option, in this context[36]. Some authors have even suggested that clinical examination combined with ultrasonography may not only identify candidates for operation but that ultrasonography may also adequately outline the extent of the arterial disease for the surgeon, making angiography of any kind unnecessary[37]. Duplex scanning is undoubtedly the most popular ultrasound technique in this respect[38] and even those who have believed duplex scanning and IVDSA to be comparable have preferred the former on grounds of cost efficiency, speed and repeatability[39]. Others have found duplex scanning to be comparable to conventional angiography, still the gold standard for most people, in a prospective study. The ultrasound technique in good hands may be just as accurate as conventional angiography in assessing stenosis and even more useful in assessing plaque characteristics[40].

In conclusion, there would seem at this time to be adequate evidence in the literature to show that IVDSA is relatively hazardous and inaccurate in most centres. It would seem to have little place in either the screening of patients with possible extracranial carotid artery disease or in pre-endarterectomy assessment. It may be that digital subtraction technology is better reserved for use with 'conventional' intra-arterial injection of contrast agent[41–43].

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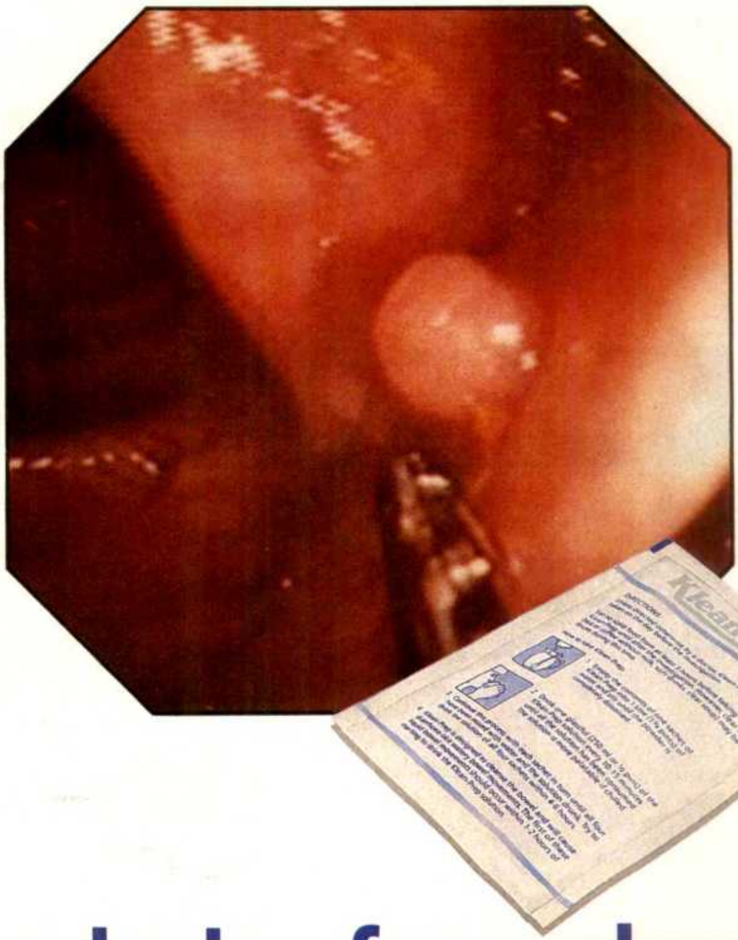

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Ten-year review of non-ruptured aortic aneurysms

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Between 1978 and 1987, 587 cases of abdominal aortic aneurysm were operated on in the Vascular Unit of the Royal Infirmary of Edinburgh. Over this ten-year period there was a dramatic increase in the number of patients treated. Rupture had occurred in 278 patients. Of the 309 patients with non-ruptured aneurysm 175 were asymptomatic, 84 were symptomatic and 50 were acutely symptomatic. Two hundred and fifty-nine patients underwent elective operation and the 50 acutely symptomatic patients were operated on as emergencies. The overall mortality for the non-ruptured series was 2·9 per cent. The mortality in patients undergoing elective surgery was 1·9 per cent (1·1 per cent in asymptomatic and 3·6 per cent in symptomatic patients) and 4·0 per cent for patients undergoing emergency surgery.

Keywords: Non-ruptured aortic aneurysm

Recorded deaths from abdominal aortic aneurysm in England and Wales have shown a progressive and linear increase over the past 30 years[1]. They now account for 1·7 per cent of all deaths in men aged 65–75 years and show a particular increase in elderly women[2]. Without surgery the mortality for patients presenting with ruptured abdominal aortic aneurysm approaches 100 per cent[3]. In those who are operated upon following rupture, mortality rates of 40–60 per cent have been reported[3,4] and these can be improved in a specialized unit[5].

It has been suggested that the survival of patients with abdominal aortic aneurysm could be improved by early detection, appropriate selection and elective aneurysm repair before rupture supervenes. This depends upon an acceptable operative mortality being achieved. The purpose of the present study was to evaluate the outcome of operations for non-ruptured aneurysms of the abdominal aorta carried out over a ten-year period.

Patients and methods

The patients included in this study comprised all those with non-ruptured aneurysm of the abdominal aorta operated on in the Royal Infirmary of Edinburgh during the period January 1978–December 1987. The Vascular Surgery Unit of the Royal Infirmary of Edinburgh was formally established in 1982, before which the surgeons worked in separate general units. Approximately 85 per cent of referrals came from the Lothians area and the remainder from adjacent Health Board areas. The overall catchment population is approximately 1·2 million.

Patients with aneurysms of the thoracic aorta, aortic dissection, acute thrombosis, frank rupture or evidence of blood outside the aortic lumen were excluded from the analysis and the remainder allocated to one of three groups. (1) elective asymptomatic – patients admitted non-urgently, without signs or symptoms referrable to the aneurysm, for planned elective surgery; (2) elective symptomatic – patients admitted non-urgently or as emergencies, with symptoms referrable to their aneurysm but without evidence of rupture and not deemed to require urgent exploration; (3) acute symptomatic – patients admitted as emergencies without signs of rupture but with sufficient symptoms or signs to merit urgent exploration within 24 h of admission. Subsequent operation showed there had been no leakage of blood outside the aortic lumen in these patients.

The data were obtained from unit statistics assembled annually for the Lothian Surgical Audit and checked against operation books and individual case records.

During the study period the vast majority of patients were assessed preoperatively by one of two consultant anaesthetists. Patients who had been judged to have significant risk factors, e.g ischaemic heart disease, systemic arterial hypertension or chronic respiratory disease, were admitted well in advance of surgery. Hypertension and poor respiratory function were improved by drug therapy and/or physiotherapy. Patients with a history of heart disease (myocardial infarction, left ventricular failure, or electrocardiograpic evidence of infarction or ischaemia or left ventricular hypertrophy) were either cardiologically assessed or, in recent years (1985–87), submitted to formal radionuclide ventriculography to obtain a value for left ventricular ejection fraction (LVEF) as an assessment of left ventricular function. Those with an LVEF >40 per cent were operated on with direct arterial and central venous pressure monitoring. Patients considered to be at risk of rupture who had surgery despite an LVEF between 30 and 40 per cent had pulmonary artery pressure monitoring via a Swan-Ganz catheter. Patients with small asymptomatic aneurysms and an LVEF <30 per cent had their operation deferred.

Antibiotic prophylaxis was used in every case, beginning either 24 h preoperatively or peroperatively, and continued for 4 days. The majority of patients were anaesthetized by one of two consultants or by a senior registrar who was directly supervised by one of the consultants All operations were performed or directly supervised by a consultant vascular surgeon. Eighty-six per cent of the patients in the second half of the study period received combined low thoracic extradural and general anaesthesia, the extradural anaesthesia being continued by an infusion for up to 36 h postoperatively. This technique offered excellent stability of arterial blood pressure, lower limb vasodilation and wound analgesia. After surgery the patients were managed, breathing spontaneously, in the vascular ward using continous direct cardiovascular monitoring and constant high dependency nursing supervision for up to 24 h. No specific prophylaxis against acute renal failure was used routinely, other than appropriate circulatory filling with blood, crystalloid and colloid according to need Patients were electively admitted to the intensive care unit when postoperative ventilation was required, usually for significant respiratory disease, and on the rare occasions when pulmonary artery pressure was being monitored

Results

Three hundred and nine patients underwent operation for non-ruptured aneurysm in the 10-year study period. A striking progressive increase in the number of patients operated on is shown (*Figure 1*) which mirrors an increasing referral rate for ruptured aortic aneurysm[5]. Ninety-one operations were performed in the first half and 218 in the second half of this period. The age and sex distribution of patients is shown in *Figure 2*, the mean age being 68 years (range 43–84) and the male:female ratio 4:1.

Two hundred and fifty-nine operations were performed electively, of which 175 were for asymptomatic and 84 for symptomatic aneurysms. Fifty patients had emergency procedures for symptomatic aneurysms.

Aneurysm dimensions were established by ultrasound, computed tomography or intraoperative measurement, the mean maximum transverse diameter being 6·4 cm (range 3·2–15·0 cm). No significant difference in the composition of the clinical groups with regard to aneurysm size was noted.

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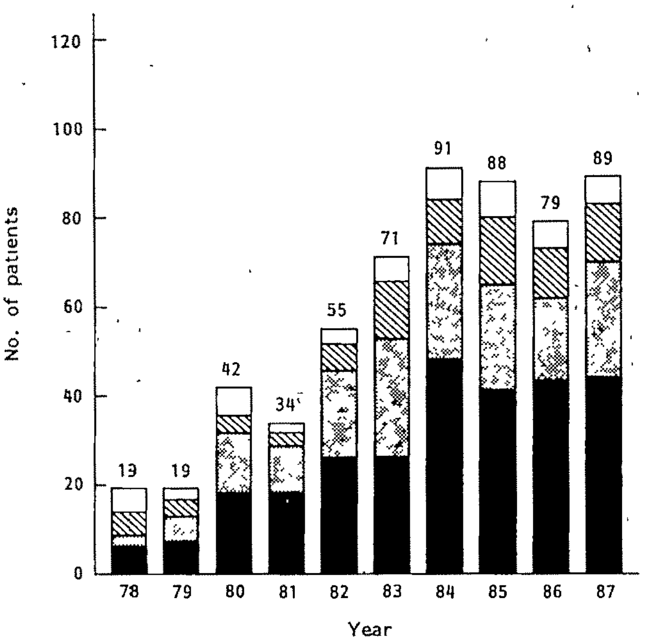

Figure 1 *Number of aneurysm operations for the years 1978–87.* ■, *Rupture;* □, *asymptomatic;* ■, *elective symptomatic,* □, *acute symptomatic*

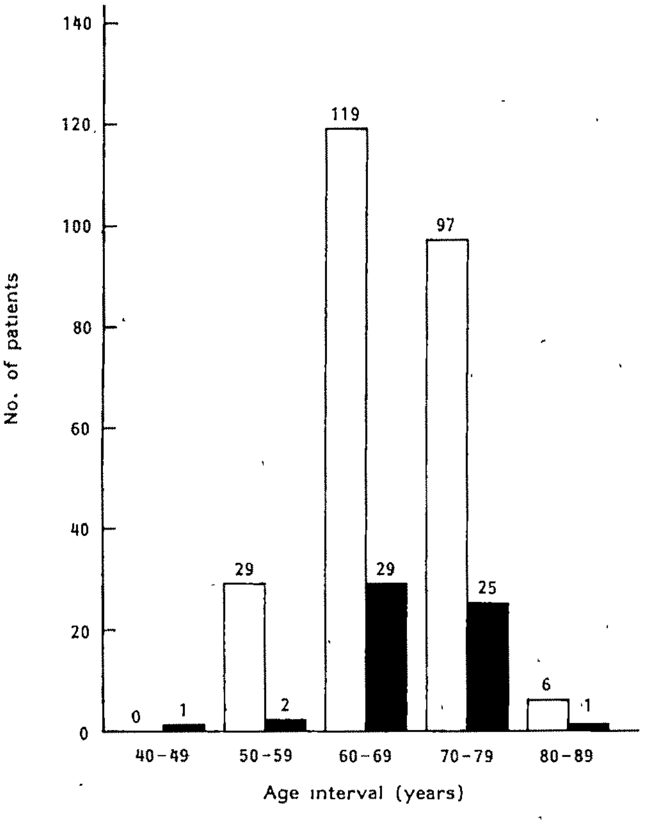

Figure 2 *Age and sex distribution of 309 patients with non-ruptured aneurysms.* □, *Men,* ■, *women*

The aneurysm extended above the renal arteries in only four patients and was confined to the infrarenal aorta in 97·5 per cent of cases. The iliac arteries were aneurysmal in 85 patients (27 per cent).

Fourteen aneurysms were diagnosed as inflammatory of which ten were symptomatic Of the 134 patients with symptomatic aneurysms, 63 per cent presented with abdominal pain, 34 per cent with back pain, 6 per cent with limb pain and 2 per cent with limb paresis.

Symptoms indicative of occlusive peripheral arterial disease were seen in 19 per cent of patients. Aortography to assess the proximal extent of the aneurysm and the distal circulation was performed in 31 patients, nine of whom were found to have additional peripheral aneurysms, five femoral and four popliteal.

Operations and grafts (Table 1)

In 76 per cent of patients a transverse incision was used, a vertical incision in 21 per cent and a paramedian in 3 per cent. All patients had a laparotomy, but in seven no graft was inserted. One hundred and ninety-three patients (62 per cent) received bifurcation grafts and 109 (35 per cent) received tube grafts. Six patients also had renal revascularization procedures for correction of renovascular hypertension or preservation of renal function. In two of these patients, in whom the aneurysm extended above the renal arteries, a kidney was temporarily removed and cooled. After the insertion of a Dacron® tube graft (du Pont), the kidney was transplanted to the iliac fossa. Of the seven patients who did not have a graft inserted, two had aneurysms extending well above the renal arteries, three had difficult access to the aorta owing to dense adhesions from previous surgery, one patient with acute symptoms had intestinal infarction and one patient died from an intraoperative myocardial infarction before insertion of the graft. After operation 65 per cent of patients were returned directly to the vascular ward (with high dependency nursing care) and 35 per cent were managed on an intensive care unit. Twenty-three patients underwent a second operation during the same admission, ten for control of intra-abdominal or wound bleeding, two for ischaemic colon, five for insertion of a Teflon®-Silastic® arteriovenous shunt for haemodialysis and six for lower limb ischaemia (graft thrombectomy, femoral embolectomy, refashioning of one limb of a bifurcation graft, popliteal thrombectomy and a femoropopliteal crossover graft), with no resultant amputations.

Outcome (Table 2)

Nine patients died within 30 days of operation, seven following the successful insertion of a vascular prosthesis and two following laparotomy without aortic replacement. The cause of death in those patients receiving a graft is shown in *Table 3*. No inpatient deaths occurred after 30 days.

One hundred and six patients made an uneventful recovery following operation. In the remainder, frequent causes of postoperative morbidity included chest infection, myocardial infarction, congestive cardiac failure and renal failure (*Table 4*).

The mean hospital stay for patients undergoing aortic reconstruction was 12 days, 30 per cent requiring additional convalescent care.

Aneurysm bacteriology

Twenty positive cultures were obtained from the 200 patients who had samples taken from within the aortic sac. Organisms

Table 1 *Nature of operation*

Operation	Number of patients
Tube graft	109 (35)
Bifurcation graft	193 (62)
Aortobi-iliac	137 (44)
Aortobifemoral	14 (4)
Aortoiliac/femoral	16 (5)
Unspecified	15 (5)
+ Distal extension	10 (3)
Aortoiliac + crossover	1 (<1)
Open and close (no graft)	7 (2)
Total	309 (100)

Values in parentheses are percentages

included *Staphylococcus aureus* and *Staphylococcus albus*, *Escherichia coli*, *Streptococcus viridans*, *Clostridium perfringens* and *Bacteroides fragilis*. No evidence of graft infection was seen during the early postoperative period and, in the two patients who died of sepsis, organisms isolated from blood cultures showed no relationship to those previously isolated from the aorta.

Discussion

The natural history of unoperated abdominal aortic aneurysm is difficult to establish and most studies to date have been retrospective[6,7]. Szilagyi *et al.* showed that 43 per cent of patients who did not have surgery because of severe coexistent disease subsequently succumbed from rupture of their aneurysm[7]. Aneurysms are reported to grow at approximately 0·5 cm per annum[8] and the risk of rupture increases as the aneurysm enlarges. Patients generally become less fit with advancing age, a further factor which favours early elective surgery. Nevertheless, such surgery can only be justified if the risk of death or disability from operation is small.

Evidence continues to accumulate that abdominal aortic aneurysm is an increasing problem[9,10] and that the mortality from this condition, if calculated from hospital data, is likely to be grossly underestimated. A recent large Swedish post mortem study suggested that mortality may be as high as 94 per cent if deaths in the community are included[11].

It is difficult to identify objectively the particular factors contributing to the improved outcome for this condition in our unit. In other centres, improved results of elective aneurysm surgery have been accredited to careful selection of patients, based on cardiac function assessed by radionuclide angiography[12] or dipyridamole thallium scanning[13]. While we have not routinely measured ejection fraction on all patients, such measurements have been applied selectively in patients with clinical evidence of significant cardiac dysfunction. All patients undergoing either elective or emergency aneurysm surgery were monitored by arterial pressure line, central venous pressure line and infrequently by Swan-Ganz catheter. This policy may in part be responsible for our survival results and may be compared with the experience of Whittemore *et al.*[14] who routinely monitored Swan-Ganz catheter pressures in patients undergoing such surgery. Several authors[15,16] have suggested that the use of a greater proportion of tube grafts can reduce mortality and it is worthy of note that Makin[15] used tube grafts in 84 per cent of his cases. In contrast, we have used tube grafts for aortic replacement in only 35 per cent of cases. This may reflect a lower threshold for the insertion of a bifurcation graft, which in our hands has not been associated with a significantly different blood loss or mortality. It is frequently technically easier to insert a bifurcation graft into the iliac arteries than to struggle with calcified atheroma at a lower aortic anastomosis. Finally, it has been suggested that prior coronary artery bypass grafting in appropriate cases can protect patients from postoperative myocardial infarction and thereby improve mortality rate[17]. In the present series, no patient underwent prior coronary bypass grafting.

The present study confirms the rising surgical workload from aortic aneurysm. The age and sex distribution and incidence of intercurrent disease was similar to that in other published series. The operative mortality for elective surgery was 1·9 per cent and that for emergency repair of symptomatic aneurysms was 4·0 per cent which compares favourably with most reported series (*Table 5*) and is in stark contrast to the results for ruptured aneurysm, which in this unit has averaged 28 per cent over the past 5 years[5]. The low mortality and morbidity herein reported lends further support to a policy of elective repair of abdominal aortic aneurysm before rupture ensues. However, despite increased awareness of the disease, approximately one-third of all patients admitted with rupture remain undiagnosed until the event[21].

Life expectancy following repair of abdominal aortic aneurysm is similar to that of matched population controls[22]. Even in 80-year-old patients a reasonable improvement in life expectancy can be expected assuming even the least favourable

Table 2 *Operative mortality*

Group	Number of patients	Number of deaths
Overall	309	9 (2·9)
After insertion of graft	302	7 (2·3)
Elective operation	259	5 (1·9)
asymptomatic	175	2 (1·1)
symptomatic	84	3 (3·6)
Emergency operation	50	2 (4·0)

Values in parentheses are percentages

Table 4 *Causes of major postoperative morbidity*

	Number of patients	Number of deaths
Chest infection	105	—
Myocardial infarction	7	2
Congestive cardiac failure	16	4
Cardiac arrhythmia	16	1
DVT/pulmonary emboli	2	—
Renal failure (requiring dialysis)	5	3
Sepsis	2	2
Cerebrovascular accident	2	—
Spinal cord ischaemia	2	—
Gut ischaemia	3	1
Prolonged ileus	3	—
Coagulopathy	2	2

Some cases have multiple entries

Table 3 *Cause of death in patients receiving grafts*

Sex	Age (years)	Operation	Time to death (days)	Cause of death
M	70	ABG	4	MI/CCF
F	69	Tube graft, left renal autotransplant, right nephrectomy	3	Multisystems failure/sepsis
M	70	ABG + re-laparotomy	3	MI/CCF
M	78	ABG	<1	MI
M	84	ABG	5	Aspiration
M	64	Tube graft	11	Sepsis
F	74	Tube graft	20	Renal failure

ABG, aortic bifurcation graft; MI, myocardial infarction; CCF, congestive cardiac failure

Table 5 *Operative mortalities in reported series*

Reference	Origin	Year	No of patients	Elective (%)	Acute (%)	Rupture (%)
Crawford[18]	Houston	1981	920	(1·43–18)		23
Diehl[19]	Cleveland	1982	557	5 1*		26
Fielding[20]	Birmingham	1981	528	8	19	42
Makin[15]	Nottingham	1983	159	10	—	50
Castleden[2]	Perth	1985	478	4	31**	
Harris[3]	Toronto	1986	90	3	27	37
Campbell[4]	Oxford	1986	153	4·2	16·7	55·8
Jenkins[5]	Edinburgh	1986	196	—	—	28
Present series		1988	309	1 9	4·0	—

X Including acute, ** including rupture

variables in regard to elective surgery[1]. Furthermore, Bowers and Cave[23], using actuarial analysis in a defined closed community, have shown elective surgery to produce a 40 per cent improvement in observed 5-year survival of patients with abdominal aortic aneurysms when compared with either conservative management or surgery following rupture. This provides additional support for a policy of elective repair. A long-term follow-up study of this series of patients is currently underway.

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Long term outcome after resection of the first rib for thoracic outlet syndrome

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A total of 112 first ribs in 103 patients were resected over 11 years for thoracic outlet syndrome. Seventy-seven patients (84 operations) were followed up for 2·5 years or more to assess the long term results of this procedure and the factors affecting them. One month after surgery 52 per cent of limbs were asymptomatic and 77 per cent were at least improved. A follow-up examination was performed, on average 6·1 years after the operation, by two independent examiners. This evaluation showed a permanent success rate of 37 per cent among 84 limbs examined. These long term results compare unfavourably with previously published data. The reason for the poor final outcome seemed to be difficulty in selecting patients for the operation. This was not aided by any of the preoperative tests. Patients in this study were evaluated by independent examiners, and only a total absence of preceding symptoms was accepted as the criterion for success. We emphasize the importance of unbiased evaluation and long term follow-up.

Keywords: Thoracic outlet syndrome, first rib resection, observer bias

Thoracic outlet syndrome (TOS) is a symptom complex caused by compression of neurovascular structures as they leave the thoracic cage through its narrow upper aperture. The first rib is generally responsible for this compression since scalenotomy does not produce permanent relief[1,2]. The operation of choice is the transaxillary removal[3] of the first rib, fibromuscular bands and cervical rib, when present[4] Many surgeons using this method have reported good to excellent primary results in between 80 and 99 per cent of patients[2–15] Failure to obtain the anticipated relief after resection of the first rib is usually due to inaccurate diagnosis and, consequently, inappropriate surgery[16]. Assessment problems also occur after surgery because no objective method is available for the evaluation of outcome[17]. The aim of the present study was to evaluate the long term outcome after resection of the first rib. A follow-up study was done 2·5 to 13·5 years after first rib resection by performing a thorough clinical evaluation and cervical X-ray examination. To minimize observer bias this was done by two independent investigators.

Patients and methods

A total of 112 first rib resections was carried out on 103 consecutive patients in the Fourth Department of Surgery, Helsinki University Central Hospital during an 11-year study period up to the end of 1985 The mean age of the patients was 37 years (range 19–61 years) and the female·male ratio was 58:45. All patients were initially examined by a vascular surgeon. A cardiologist, a neurologist and an orthopaedic surgeon were consulted in selected cases Positional provocation in a vascular laboratory, functional angiography and electroneuromyography were subsequently performed in 33 patients during the first years of the study The decision to resect the first rib was largely based on clinical judgement with emphasis on a typical history and the exclusion of other potential causes of radiculopathy. A transaxillary approach was always used for the resection of the first rib, which was performed extraperiosteally in all but the first 17 patients. Patients were usually discharged on the third or fourth postoperative day and were advised neither to raise the arm above the shoulder for 4 weeks nor to use it for lifting or exertion. The surgeon carried out a routine examination about a month after operation and patients were then usually allowed to return to work without restrictions

The long term follow-up examination was made on average 6 1 years (range 2·5–13 5 years) after operation None of the surgeons involved in the preoperative examination, selection of patients, surgery, or early postoperative follow-up participated in the long term follow-up examination A questionnaire was sent to the patients 1 month before this examination. Two independent examiners, consultants in neurology and in physical medicine and rehabilitation respectively, from another university hospital undertook this clinical examination, which lasted 30 min or more, and at which data were simultaneously recorded by two nurses.

The examination comprised systematic assessment of the movements and mobility of the cervical spine, shoulder girdles, elbows, wrists and hands Sensory modalities and reflexes of the upper arms were also tested In addition to the classical TOS provocation tests, Adson's, Wright's and Eden's tests, Roos's exercise test was also performed. Both subclavian arteries were auscultated and distal pulses palpated Status was defined as abnormal if there were definite abnormal findings in either the active or passive movements tested or in the muscle and nerve functions tested The cervical spine was radiologically examined to assess the stump of the first rib.

The association of various pre- and postoperative factors with postoperative outcome was retrospectively assessed The value of preoperative tests in terms of different outcome was assessed using the χ^2 test or Fisher's exact test as appropriate

Results

During follow-up three patients died from causes unrelated to TOS. Of the remaining 100 patients with 108 resected first ribs, 77 with 84 resected ribs attended the follow-up examination.

At the 1-month postoperative examination, preoperative symptoms were found to be reduced in 83 (77 per cent) of 108 limbs, with 56 (52 per cent) of limbs totally asymptomatic. At long term follow-up, 31 (37 per cent) of 84 limbs remained asymptomatic. In one patient the vascular clamps used for controlling profuse bleeding had caused permanent damage to the brachial plexus. Two others had developed sequelae to venous thrombosis A further 23 (27 per cent) limbs had hypoaesthesia or dysaesthesia of the inner aspect of the upper arm due to an intercostobrachial nerve lesion.

If symptoms had been provoked preoperatively by work, had been at their worst during the night, had been associated with neck pain or had previously led to scalenotomy, the first rib resection was more often unsuccessful than in patients without such associations (*Table 1*). There was no difference between the patients with long term success and those with remaining symptoms in terms of age or duration of symptoms The mean age at operation was 38 years (range 24–61 years) in the successful group and 37 years (range 19–54 years) in the

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Table 1 *Preoperative characteristics with long term outcome*

Characteristics	Asymptomatic ($n=31$)	Symptomatic ($n=53$)
Men	13 (42)	22 (42)
Earlier trauma	3 (10)	9 (17)
Heavy labour	12 (39)	14 (26)
Provoked by work	6 (19)	33 (62)***
Worst immediately after work	3 (10)	12 (23)
Worst during the night	6 (19)	29 (55)**
Neck pain	11 (35)	36 (68)***
Previous physiotherapy	17 (55)	40 (75)
Previous scalenotomy	1 (3)	12 (23)*

Values in parentheses are percentages; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$ (χ^2 test or Fisher's exact test as appropriate)

Table 2 *Abnormal findings in preoperative tests with long term outcome*

	Percentage of patients with abnormal preoperative findings	
Test	Asymptomatic	Symptomatic
Vascular laboratory thoracic outlet syndrome provocation	38	45
Functional angiography	71	68
Electroneuromyography	36	55
Roos's test	87	91
Adson's, Eden's or Wright's test	87	86

group with residual symptoms. Duration of TOS was 24 months (range 3–52 months) and 31 months (range 4–132 months) respectively. Preoperative tests performed on selected patients were not reliable predictors of outcome (*Table 2*).

The length of the residual portion of the first rib did not affect the results. The mean stump length was 27 mm (range 0–62 mm) in the group with long term success and 29 mm (range 0–81 mm) in the group with residual symptoms. The long stumps were associated with the early intraperiosteal resections.

Discussion

A classification of surgical results into categories such as fair, improved or good may easily be biased, especially if done by the operating surgeons. Therefore, we tried to use as clearcut a definition as possible for classification when using retrospective data. With this method the operative success rate was only 52 per cent, far lower than in other series. If, however, not only asymptomatic patients but also those showing improvement, as defined both by the patient and by the examining surgeon, were accepted as being good results, an immediate 'success' rate of 77 per cent was achieved. This latter result is nearer those found in other short term series where success rates are typically 80–99 per cent[2–15]. It is likely that, in the present study, there was a significant number of patients with initial symptoms due to causes that were unlikely to be relieved by removing the first rib[16].

It is hard to assess success when there are no satisfactory objective tests for comparing preoperative and postoperative states[17]. Carroll and Hurst[18] noted that some patients who were reported by their surgeons as having improved were subsequently described by others as not having been helped by surgery for TOS. In order to avoid such bias, independent observers were invited to do our long term follow-up examinations. Little more than one-third of patients had a true, permanent success.

Unfortunately, no single predictive characteristic for success was found in the clinical history. Furthermore, none of the preoperative tests used in this study seemed to be of any clinical value. This has already been observed by others[19]. Vascular laboratory studies, functional angiography and classical TOS provocation tests, i.e. Adson's, Eden's and Wright's tests, are all aimed at disclosing vascular compression, which is present only in 1–2 per cent of all patients with TOS[17]. A lack of uniform neurophysiological findings means also that there is no reliable neurophysiological method in patients with TOS[20–22].

The high frequency of prolonged dysaesthesia in the area innervated by the intercostobrachial nerve accords with the observation of an area of permanent numbness in 20–27 per cent of limbs in other series[2,23]. Although intraperiosteal resection of the first rib might be linked to regrowth of the rib, the length of the stump was not related to the long term outcome in the present series.

The results of this study suggest that resection of the first rib is the treatment of choice for only a limited number of carefully selected patients. The selection, however, is very difficult since no objective tests of proven value exist.

Acknowledgements

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Unusual cause of thoracic outlet syndrome

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Case report

A 22-year-old builder presented with a 4-year history of recurrent pain in the right wrist, a 3-month history of paraesthesia radiating from the right wrist to the elbow, and intermittent right-sided neck pain, all of which were exacerbated by sneezing. The symptoms began when he started a new job which involved heavy lifting.

On examination he was generally fit. The upper limb pulses were present but with a reduced volume in the right radial. The systolic blood pressure was lower by 20 mmHg when measured in the right arm. A loud bruit was audible over the right subclavian artery. There was no muscle wasting in the arm but there was reduced power in the intrinsic muscles of the hand, together with reduced perception of pin-prick and light touch in the seventh and eighth cervical nerve root sensory distribution. Radiographs excluded a cervical rib. Electromyography identified a conduction abnormality in the ulnar nerve, not localized to the elbow. An intravenous digital subtraction angiogram showed a kink in the right subclavian artery at the first rib (*Figure 1*).

Right first rib resection was carried out via a standard axillary approach[1]. An abnormal swelling at the origin of the subclavian artery gave the impression of a haematoma around the artery. Median sternotomy was performed and the innominate artery was controlled. The first thoracic nerve root was defined within the thorax and the lesion previously thought to be a haematoma was found to arise within the nerve root. The mass was excised, a drain was inserted and the chest was closed. Histopathology of the specimen revealed a benign schwannoma with degenerative features (*Figure 2*). The patient recovered and was discharged home.

Discussion

Pang and Wessel found no reports of brachial plexus tumours causing thoracic outlet obstruction in a review of 159 papers between 1846 and 1987[2]. Lusk *et al.* reported 147 patients with primary tumours of the brachial plexus in the world literature since 1886[3]. In a series of 600 brachial plexus lesions between 1969 and 1985, 384 were operated upon and 57 were tumours[3]. Eight of these were benign schwannomas. Presentation was usually as a painless, palpable, mass with mild or no neuronal loss, which contrasts with the present case in which the tumour was out of reach and caused the pressure symptoms of thoracic outlet obstruction. Five of the eight schwannomas were located on the fifth or sixth nerve root, or on the upper trunk. The remainder were on the lower trunk or on the lateral and the medial cords. In another review of 480 benign schwannomas, Gyhra *et al.* found only 24 arising from the brachial plexus[4]. A case report was given of such a patient with intrathoracic extension of the tumour which had not been previously reported. The difficulties of diagnosing brachial plexus tumours before operation have been emphasized, especially when these tumours are inaccessible to palpation[5,6].

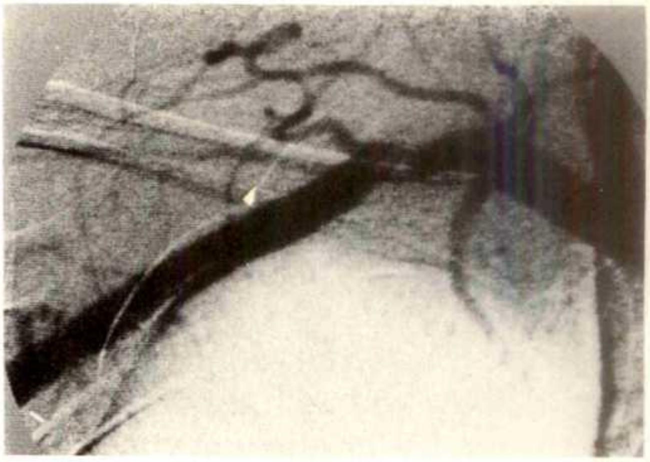

Figure 1 *An intravenous digital subtraction angiogram showing a kink in the subclavian artery on abduction of the right arm*

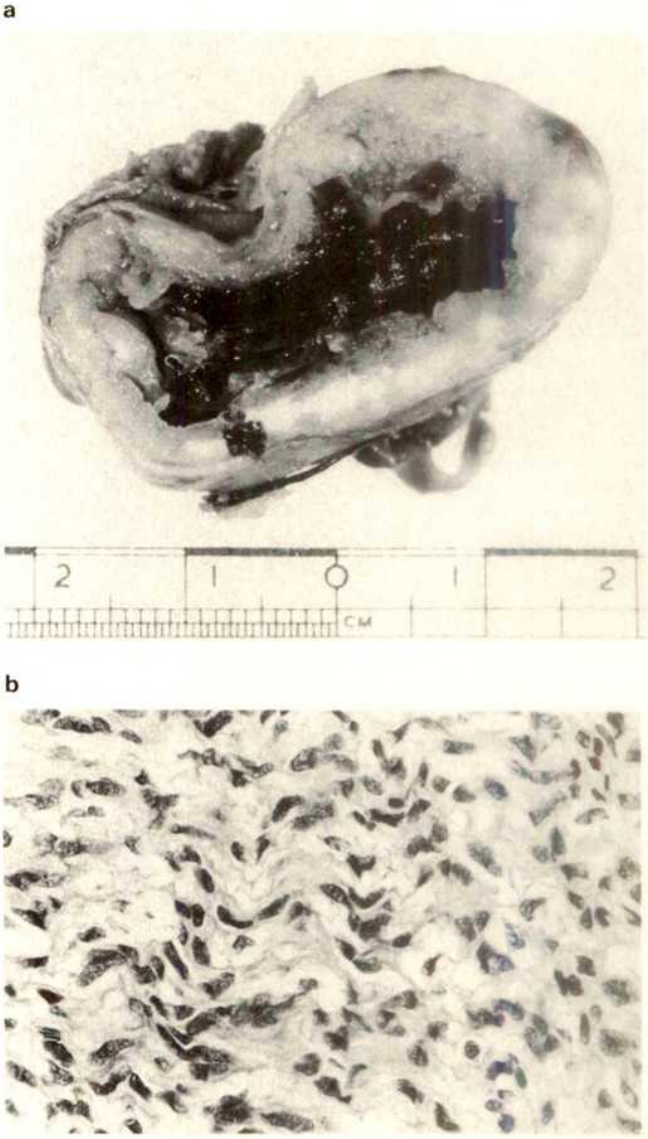

Figure 2 **a** *Benign cystic schwannoma containing clotted blood.* **b** *Microscopic appearance of benign schwannoma with degenerative features. Nerve fibres were present in the capsule of the tumour*

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Thoracic outlet syndrome caused by a schwannoma of the brachial plexus is exceptionally rare. We have found no reports of such a presentation in the literature.

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Combined internal and external biliary fistulae treated by percutaneous cholecystlithotomy

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Spontaneous biliary fistulae are rare, occurring in approximately 3 per cent of all patients undergoing biliary surgery, and they usually communicate with the duodenum[1,2].

Case report

An 84-year-old man was referred with a 3-month history of a discharging sinus in the right hypochrondrium. The patient had been admitted 1 year previously with an episode of acute cholecystitis; gallstones were confirmed on ultrasound scan and he settled on conservative treatment. The patient also had obstructive airways disease, congestive cardiac failure and chronic renal failure. A sinogram revealed cholecystcutaneous fistulae, multiple large gallstones and cholecystduodenal fistulae; the remainder of the biliary system appeared normal (*Figure 1*). The tract was too small and tortuous to allow cannulization.

In view of the patient's poor medical condition, direct exploration of the external cholecystcutaneous fistulae was undertaken under local anaesthesia. A small 3-cm incision was made after the tract was dilated, and six large gallstones were removed using a Desjardin's forceps. A 12 Fr Fogarty catheter was inserted, the catheter was brought out through a separate skin incision, and a corrugated drain was placed in the fistula tract. Postoperative recovery was uneventful, and a catheter cholangiogram at 9 days showed a patent biliary system with contrast draining freely into the duodenum. At review, 3 months later, the patient was well, the fistula tract had closed and an oral cholecystogram was normal.

Discussion

In 1670, Thilesus described the first external biliary fistula and, in the 19th century, when the condition was common, Courvoisier reported 169 cases of spontaneous external fistula formation[3,4]. However, only 45 further cases have been reported to date with only nine cases reported from 1944 to 1985[5]. The dramatic fall in incidence is attributable to the advent of modern biliary tract surgery.

Spontaneous biliary fistulae are usually the result of acute suppurative cholecystitis, and they drain into the duodenum in 75 per cent of all cases. Fistula formation into the colon, bronchial tree, stomach and urinary tract have also been reported but these fistulae are extremely rare[6–8]; only one case of combined internal and external biliary fistulae has been reported to date[5]. In that case, the patient who was otherwise healthy was treated successfully by cholecystectomy and excision of the fistulous tracts. However, in high risk patients, percutaneous removal of the stones should be considered, and with an existing tract to the gallbladder endoscopic access may be feasible if the tract can be dilated. The presence of a patent cystic duct and distal biliary tree following the procedure should ensure that the cholecystcutaneous fistula closes spontaneously when the drain is removed.

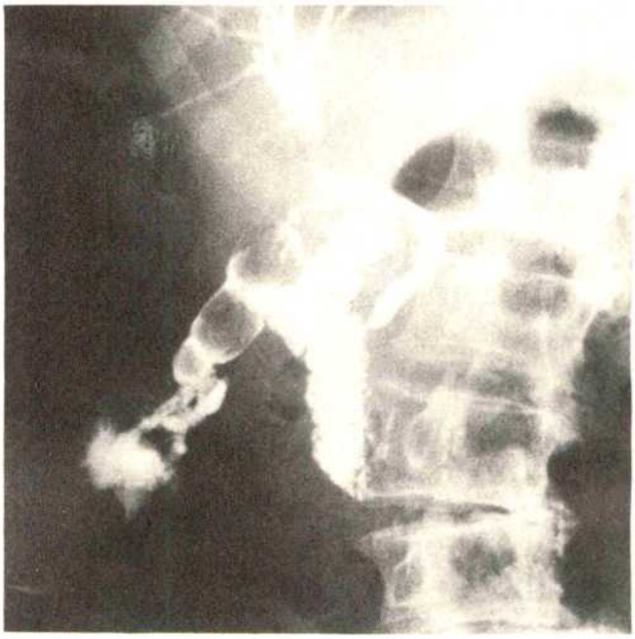

Figure 1 *Contrast fistulogram showing multiple gallstones in the gallbladder and fistulae to the skin and duodenum*

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Attachment of indium-111 labelled endothelial cells to pretreated polytetrafluoroethylene vascular grafts

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This study investigated the effect of different surface coatings on endothelial cell attachment to polytetrafluoroethylene (PTFE) vascular grafts. Small segments of PTFE vascular grafts were precoated with one of a number of substances: gelatin, poly-l-lysin, fibronectin, or collagen type I, III or IV. Indium-111 labelled endothelial cells were then seeded on to the grafts and left for either 10, 30, 60 or 120 min. The unattached cells were removed and the degree of cell attachment was calculated. All coatings were significantly better at enhancing endothelial cell attachment at all times compared with controls, and fibronectin was significantly better as a coating material than any other material used. By pretreating with a substance such as fibronectin, the number of endothelial cells attaching to PTFE vascular grafts can be greatly increased, thereby enhancing the cell seeding process.

Keywords: Vascular grafts, endothelial cells, cell seeding

Autogenous saphenous vein remains the best small-calibre arterial substitute at the present time. However, it is often unavailable or unsuitable and in this situation prosthetic grafts offer the only alternative. Although satisfactory results have been obtained using prosthetic grafts in larger vessels such as the aorta, results using prosthetic grafts in the infrainguinal region, especially below the knee, have been disappointing. The absence of a functional endothelial cell monolayer on the luminal surfaces of these small-diameter prostheses is one of the reasons that they have failed to live up to their expectations[1]. Recent studies in animal models have shown that seeding endothelial cells on to the luminal surface of prosthetic grafts before implantation accelerates graft endothelialization, reduces luminal thrombus formation and improves short-term patency[2,3]. In humans, however, the number of endothelial cells that can be harvested from the limited lengths of donor vessel available is considerably lower than in animal models[4] and this has hampered progress with human endothelial cell seeding. Various substances such as gelatin and fibronectin are known to enhance cell attachment and subsequent spreading on tissue culture plastic[5]. The aim of the present study was to optimize the use of the limited number of endothelial cells available by improving their attachment on to the graft material using various surface coatings. Human umbilical vein endothelial cells were used for this purpose.

Materials and methods

Endothelial cell cultures

Endothelial cells were harvested from human umbilical veins. Umbilical cords were collected within 24 h of delivery and all clamp marks and needle holes were removed. The umbilical vein was cannulated at either end and was then flushed with 10 ml minimum essential medium (MEM) to remove any residual blood. Three-way taps were connected to the cannulae. The vein was then distended with 5 ml 0·1 per cent collagenase solution (CLS I, Worthington Biochemical, Freehold, New Jersey, USA; $CaCl_2$ 15 mmol/l) prewarmed to 37°C, and the whole cord was incubated for 15 min at 37°C. After incubation the vein was flushed through with 20 ml MEM to remove dislodged endothelial cells and the resulting cell suspension was centrifuged for 7 min at 200*g* and 4°C. The cell pellet was resuspended in 5 ml complete medium. This consisted of medium M199 containing 20 per cent fetal calf serum, 100 units/ml penicillin, 100 μg/ml streptomycin, 20 mmol/l Hepes buffer, 2 mmol/l glutamine, 1 mmol/l pyruvate (all from Flow Laboratories, Irvine, UK), 20 μg/ml endothelial cell growth supplement and 90 μg/ml heparin (both from Sigma Chemical Company, Poole, UK), and the cells were finally plated on to a 25 cm^2 tissue culture flask. The cells were incubated at 37°C in 95 per cent O_2/5 per cent CO_2 for 3–7 days until they reached confluence.

Identification of cells

Confirmation of endothelial cell identity was made by appearance at confluence using phase contrast microscopy and by confirming the presence of von Willebrand factor using a rabbit antihuman von Willebrand factor (Dakopatts, Glostrup, Denmark).

Labelling of endothelial cells

Once at confluence, the cells were harvested with 0·1 per cent trypsin in 0·02 per cent ethylene diamine tetra-acetic acid at 37°C. The trypsin was then inhibited by adding excess MEM containing 20 per cent fetal calf serum. The resulting cell suspension was centrifuged for 7 min at 200*g* and 4°C, and the cell pellet was resuspended in a small volume of serum-free medium. A mean (s.e.m.) of 1·68 (0·12) $\times 10^6$ cells was then labelled with 100 μCi ^{111}indium oxine at room temperature for 15 min. After labelling, the cells were washed three times with MEM and finally resuspended in 5 ml MEM with 10 per cent fetal calf serum in readiness for seeding. At this point a small sample of the labelled cell suspension was taken for cell counting and viability studies using trypan blue. Labelling efficiency was also determined at this time.

Preparation of graft surfaces

Expanded polytetrafluoroethylene (PTFE) vascular grafts of standard thickness (0·64 mm) and with an internal diameter of 6 mm were used. The grafts were cut into short segments and opened lengthways to expose the luminal surface. Each segment was then immobilized in a well constructed from a modified Eppendorf tube (*Figure 1*). The well allowed 0·5 cm^2 of the luminal surface of the PTFE to be exposed. All subsequent surface treatments and endothelial cell seedings were performed on this immobilized surface. Gelatin (1 per cent), poly-l-lysin (20 μg/ml), fibronectin (20 μg/ml), and collagen types I, III and IV (20 μg/ml) (all from Sigma, UK and made up in MEM) were compared as substrates for cell attachment on PTFE. One hundred microlitres of the solution to be tested were placed in a well and incubated at 37°C for 2 h. The solution was then removed and the surface was air dried before seeding. Controls were coated with MEM.

Attachment of endothelial cells to graft material

One hundred microlitres of the labelled cell suspension were added to individual wells containing graft segments with different coatings. After incubation in 95 per cent O_2/5 per cent CO_2 at 37°C for periods ranging from 10 to 120 min, the unattached cells were removed and saved (ten

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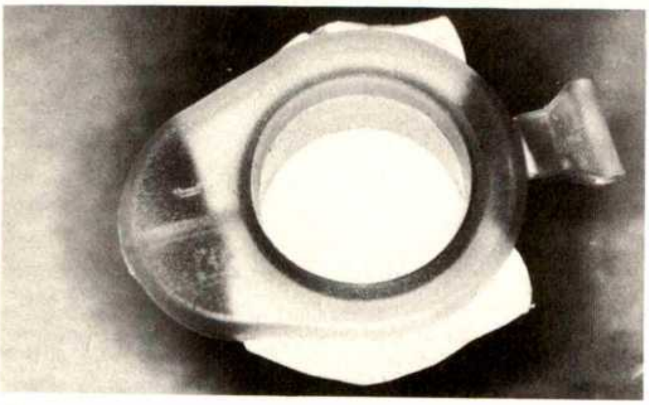

Figure 1 *Endothelial cell seeding chamber as seen from above*

separate studies were carried out on each coating for each incubation time). The graft surface was then washed gently and the washings were added to the previously removed cells. Radioactivity on the graft segments and in the unattached cells was measured. The degree of cell attachment was expressed as a percentage of the initial cell inoculum by using radiation counts in the following formula:

$$\text{Cell attachment (\%)} = \frac{\text{Counts on graft}}{\text{Counts in washings} + \text{counts on graft}} \times 100$$

Statistical analysis

All data were analysed using both a paired *t* test and Wilcoxon signed ranks test.

Results

Figure 2 shows the typical morphological appearance of endothelial cells on phase contrast microscopy, and the fluorescent localization of von Willebrand factor in the cells (*Figure 3*) confirms their identity. The mean (s.e.m.) number of endothelial cells seeded on to the graft segments was 6·7 (0·5) × 10^4 cells per cm^2. The mean (s.e.m.) labelling efficiency with indium-111 was 19(3) per cent, a figure which corresponds to that obtained by Sharefkin *et al.*[6]. The cell viability after labelling, as determined by staining with trypan blue, was always greater than 96 per cent. Although a similar number of endothelial cells was seeded on to the graft segments each time, we have expressed cell attachment as a percentage of the initial cell inoculum rather than as a finite number. More then ten times as many endothelial cells initially attached to graft coated with fibronectin compared with untreated controls ($P < 0·01$) (*Table 1*). Indeed, all coatings were significantly better at enhancing endothelial cell attachment at all times compared with controls ($P < 0·01$ for all coatings at all times except gelatin and poly-l-lysin at 10 min, where $P < 0·05$). Fibronectin was significantly better as a coating material than any other material used ($P < 0·01$ *versus* all other coatings at all times except collagen type I at 120 min, where $P < 0·05$). The time trend for endothelial attachment to PTFE using some of the coating materials is shown in *Figure 4*. Endothelial cell attachment to fibronectin-coated PTFE reached 50 per cent after 20 min and attained an apparent maximum of 60 per cent at 60 min. In contrast, on uncoated PTFE grafts, just over 5 per cent of cells attached after 20 min, doubling to 10 per cent at 1 h.

Discussion

The endothelial cell monolayer of blood vessels is non-thrombogenic, largely owing to its ability to produce prostacyclin. Unlike most other animals, humans do not endothelialize prosthetic grafts except for short distances at anastomoses[1]. Most of the graft luminal surface therefore remains relatively thrombogenic, especially just after implantation. In the canine model, autologous endothelial cell seeding of prosthetic grafts has led to a confluent endothelial cell monolayer within 4–6 weeks[7,8], with concomitant improvement in graft patency rates, even in situations of relatively low blood flow. In humans, however, there are two main obstacles to practical cell seeding. Firstly, there is a relatively low number of endothelial cells available for immediate seeding and, secondly, there is a low rate of cell retention due to poor attachment to the graft surface[9]. Because only small lengths of donor vessel are available in humans, the potential for increasing the number of cells available for immediate seeding is limited, although Jarrell *et al.* have successfully used omentum to increase the yield of endothelial cells[10]. In order to make full use of harvested cells, the surface of an ideal graft should produce efficient initial attachment.

The present preliminary study has shown that precoating PTFE grafts with fibronectin significantly improved initial

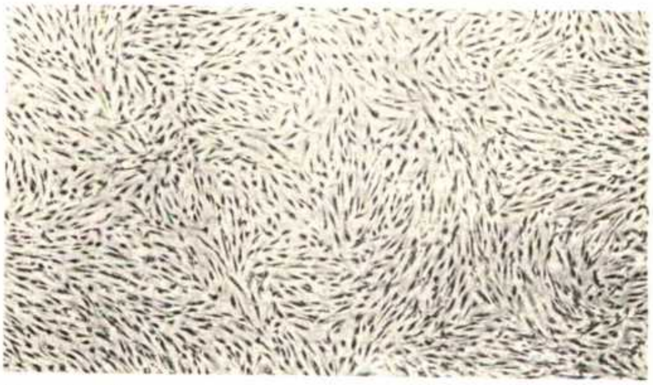

Figure 2 *Phase contrast micrograph of typical human venous endothelial cells in tissue culture (original magnification × 40)*

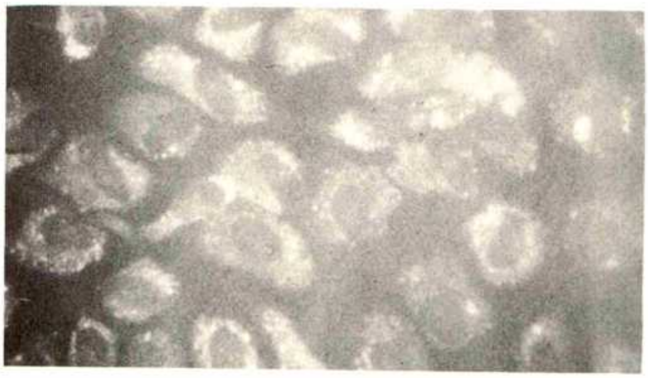

Figure 3 *Fluorescence micrograph of human venous endothelial cells stained for von Willebrand factor (original magnification × 200)*

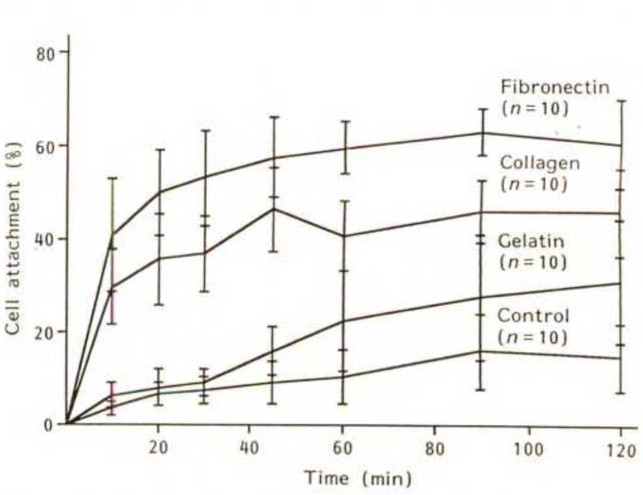

Figure 4 *The percentage attachment of endothelial cells to polytetrafluoroethylene pretreated with gelatin, collagen type I or fibronectin, and to untreated controls. Bars represent standard deviation*

Table 1 *Endothelial cell seeding on to polytetrafluoroethylene with different surface coatings. cell attachment at different times expressed as a percentage of the initial cell inoculum*

Coating	Cell attachment Time after seeding 10 min	 30 min	 60 min	 120 min
Control (uncoated)	3·6 (1 5)	7·5 (2·8)	10·4 (5 6)	14·9 (7·4)
Gelatin	6·3 (2 7)†‡	9·3 (2·9)*‡	22·5 (10·9)*‡	31·2 (17·3)*‡
Poly-l-lysin	6 3 (3·1)†‡	14·7 (7 7)*‡	22·9 (10·9)*‡	28 9 (15 2)*‡
Fibronectin	40·8 (12 2)*	53·2 (10·1)*	59·8 (5·8)*	60·8 (9 5)*
Collagen I	29·7 (8 3)*‡	37 0 (8·1)*‡	40·8 (7·5)*‡	46·2 (9·4)*§
Collagen II	21·0 (5·1)*‡	28·2 (6 9)*‡	37 7 (7 3)*‡	41·5 (7·8)*‡
Collagen III	18·5 (2·8)*‡	24·6 (5 1)*‡	37·3 (10 3)*‡	37·9 (11·1)*‡

Figures are mean (s d.); * $P<0·01$ *versus* control; † $P<0·05$ *versus* control; ‡ $P<0·01$ *versus* fibronectin; § $P<0·05$ *versus* fibronectin

endothelial cell attachment compared with controls. Collagen of all types, but type I in particular, also markedly enhanced the initial cell attachment, but to a significantly lesser degree than fibronectin. This contrasts with the results of Anderson *et al.*[11] who found that collagen was superior to fibronectin, although a truly direct comparison is not possible because they measured the absolute number of cells retained rather than the percentage, as in our study Hasson *et al.*[12] found that gelatin was as effective as fibronectin but these authors coated tissue culture plastic rather than PTFE. Although gelatin did increase attachment on to PTFE in our study, it was not nearly as effective as fibronectin. Other studies have shown that fibronectin coating is superior to PTFE alone, but comparison with other coating materials is lacking[13,14].

Fibronectin seems to be a ubiquitous glycoprotein. It is synthesized by a variety of cells, including endothelial cells, and is present in plasma. It has been shown to promote cell adhesion and spreading and has also been implicated in the regulation of platelet adhesion and aggregation. Since pretreatment of PTFE with fibronectin increases initial endothelial cell attachment, it is reasonable to suppose that it will also facilitate growth to confluence, as it does in *in vitro* tissue culture. However, this process takes time, and in the canine model up to 6 weeks are required for immediately harvested endothelial cells to achieve confluence on PTFE grafts. During this period, parts of the graft surface not covered with endothelial cells remain exposed to blood components and are potential areas for platelet accumulation. One might expect, since fibronectin increases endothelial cell attachment to grafts, that it may also increase platelet attachment on exposed graft surface. Although this has been demonstrated by Seeger *et al.*[15], short-term graft patency was not adversely affected, presumably because of the relative increase in endothelial cell coating promoted by fibronectin. Nevertheless, the exposure of fibronectin-sensitized, non-endothelial cell-coated areas of graft is a potential disadvantage which may preclude the use of this substance when a small number of cells are seeded for a short incubation time. The problem of an initially increased thrombogenicity, before the later development of confluence, could perhaps be countered by the use of antiplatelet agents or by anticoagulation[16].

Further studies of surface preparations are necessary to find the best seeding environment. To eliminate the potential adverse effects of exposed areas of graft or coating material, which may occur when implantation rapidly follows seeding, a delay would seem appropriate to try to produce a confluent endothelial cell monolayer on the graft before implantation The advantages of fibronectin as a coating material might then be utilized more fully and the disadvantage of increased platelet adherence might be avoided.

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Combined endocrine effects of LHRH agonist (Zoladex®) and tamoxifen (Nolvadex®) therapy in premenopausal women with breast cancer

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In premenopausal women with breast cancer, the use of the luteinizing hormone releasing hormone agonist, goserelin, results in the production of serum levels of oestradiol equivalent to those after surgical oöphorectomy or in postmenopausal women. The standard first line hormonal treatment for systemic breast cancer in postmenopausal women is tamoxifen. The combination of goserelin and tamoxifen in premenopausal women has been proposed. We have treated 34 premenopausal breast cancer patients with goserelin (3·6 mg) monthly and tamoxifen (20 mg) twice daily: endocrine data are available on all 34 patients. As with goserelin alone, patients on goserelin and tamoxifen showed transient stimulation of serum follicle stimulating hormone over the first 7–10 days with subsequent low gonadotrophin levels. Serum oestradiol and progesterone levels were reduced to castrate levels in all patients studied; no peaks of serum oestradiol were detected. There is no endocrinological contraindication to the use of goserelin and tamoxifen together in premenopausal women with breast cancer either as adjuvant therapy or in treating advanced disease.

Keywords: Breast cancer, premenopausal, LHRH agonist, antioestrogen, combination

The endocrine and clinical effects of the luteinizing hormone releasing hormone (LHRH) agonist goserelin as the sole initial therapy for premenopausal advanced breast cancer have been reported[1–3]. Goserelin alone produced castrate levels of oestradiol and response rates of 31 per cent, which are equivalent to those seen after surgical oöphorectomy[3].

The antioestrogen, tamoxifen, is widely used as the initial therapy in postmenopausal patients with advanced breast cancer owing to its low toxicity and proven efficacy. The combination of goserelin and tamoxifen together in the treatment of advanced premenopausal breast cancer has a definite rationale, in that having made a patient effectively postmenopausal with goserelin it would then seem reasonable to treat them as postmenopausal patients with tamoxifen. Combining goserelin and tamoxifen therapies would be an attempt to maximize the response to endocrine therapy by increasing the rate and/or the duration of response.

The use of tamoxifen alone in premenopausal patients can cause intermittent peaks of serum oestradiol[4–6] which might over-ride the effect of goserelin therapy alone. Detailed endocrinological assessment of the combination of goserelin and tamoxifen is necessary before it can be recommended for wider use. Here we report the results of 34 patients with premenopausal breast cancer treated with goserelin and tamoxifen together.

Patients and methods

Thirty-four premenopausal patients with a histological diagnosis of breast cancer have been treated with goserelin (Zoladex®, ICI Pharmaceuticals (UK), Macclesfield, UK) and tamoxifen (Nolvadex®, ICI Pharmaceuticals (UK)) in combination as an initial hormone therapy. all patients gave a written informed consent The mean age of the patients on commencing therapy was 43·8 years. median 44 years, range 28–53 years. The sites of disease are shown in *Table 1*. Of the 20 patients with metastatic disease the major sites of disease were bone (six patients), lung (eight patients), bone and lung (four patients) and viscera (two patients)

Before commencing the combination therapy all patients had a full clinical examination and skeletal survey; routine haematological and biochemical tests were carried out, and photographs of any visible diseases were taken. These investigations were repeated at 3-monthly intervals or earlier if clinically indicated. Other investigations (e g. isotope bone scan, computed axial tomographic scan) were carried out if clinically indicated

All patients received goserelin 3·6 mg by subcutaneous injection every 4 weeks, along with tamoxifen 20 mg twice a day Peripheral blood (10 ml) was obtained at the following times: days 0, 2, 8, 15, 22, 29, and weeks 8, 12, 18 and 24. The blood was placed in bottles without anticoagulant; it was centrifuged and the serum was pipetted off and frozen initially to −20°C and later to −70°C.

Sera from all 34 patients treated with goserelin and tamoxifen have been assayed for follicle stimulating hormone (FSH), luteinizing hormone and progesterone using methods previously described[2]. The endocrinology of the combined goserelin and tamoxifen therapy was compared with the previously reported endocrine data from 24 patients who received the monthly goserelin injection alone[3].

A new oestradiol assay has recently been established at the Tenovus Institute. In all the patients who received goserelin alone[3], oestradiol was measured by the old assay. Of the 34 patients who received goserelin and tamoxifen 15 had serum oestradiol measured by the old assay and the remaining 19 by the new assay. Comparison of serum oestradiol in patients on goserelin and tamoxifen *versus* those on goserelin alone is between the 15 patients on the combined therapy who had serum oestradiol measured by the old assay and the 24 patients on goserelin alone all of whom had serum oestradiol measured by the old assay.

Table 1 *Sites of disease in 34 patients who received goserelin and tamoxifen combined therapy*

	Number of patients
None (adjuvant therapy)	3
Locally advanced primary	7
Locoregional recurrence only	4
Locoregional recurrence with metastatic disease	6
Metastatic disease only	14

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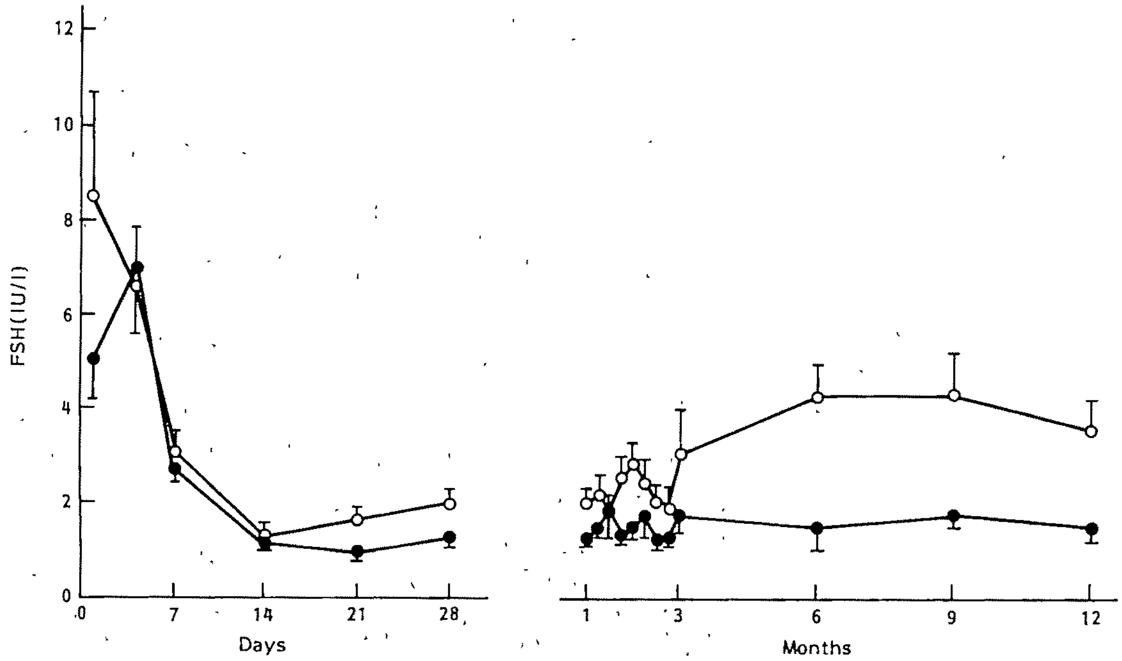

Figure 1 *Mean (s.e.m.) serum follicle stimulating hormone (FSH) levels in 34 patients treated with goserelin and tamoxifen compared with 24 patients treated with goserelin alone.* ○, *goserelin alone,* ●, *goserelin and tamoxifen*

Data on serum oestradiol from the 19 patients on goserelin and tamoxifen who had serum oestradiol measured by the new assay were not entered into the comparison between the two therapies. Data from these 19 patients were reported separately to confirm that castrate levels of oestradiol were obtained and that there were no intermittent peaks of oestradiol on therapy in these patients No correlative data between the differing oestradiol assays are therefore given in this paper except to note that the new assay gives slightly lower serum oestradiol values than the old assay Serum oestradiol concentrations were originally measured using a commercially available kit from Steronti Research Ltd. Subsequent concentrations were determined using a double antibody kit provided by Diagnostic Products Corporation, Whitney, Oxon, UK.

Patients were assessed for response to goserelin and tamoxifen by the UICC (International Union Against Cancer) criteria[7] while adhering to the British Breast Group recommendations[8] that the minimum duration of remission should be 6 months and that an external assessment of response should be carried out; 23 patients were assessable for response, while 11 patients were not assessable for the following reasons. three patients received the combination treatment as adjuvant therapy and eight patients had systemic disease which was unassessable for response by UICC criteria.

Results

Serum FSH, and oestradiol (mean and s.e.m.) levels in patients on the goserelin and tamoxifen combination are shown in *Figures 1* and *2* respectively; a comparison is made with the 24 patients who received the monthly 3·6 mg goserelin injection alone. Serum FSH levels were significantly lower in patients on goserelin and tamoxifen than in patients on goserelin alone ($P < 0.05$; Mann–Whitney U test) at all time points shown in *Figure 1* from 1 month onwards Furthermore the slight upward drift of the serum FSH level in patients on goserelin alone (*Figure 1*) does not occur with the combined therapy, and it would appear that the combination achieves better suppression of serum FSH.

Figure 2 shows that the serum oestradiol levels were decreased to the castrate range by both treatments within 3–4 weeks of the initiation of therapy. There was no difference in the serum oestradiol levels between the two treatment groups at any time from 1 month onwards.

Figure 3 shows that the mean serum oestradiol level was in the castrate range in the 19 patients on goserelin and tamoxifen who had their serum oestradiol level measured by the new assay.

No intermittent peaks of serum oestradiol were noted in any of the 34 patients receiving the combination therapy. There was a transient stimulation of serum luteinizing hormone over the first 7–10 days (peak mean 14·0 International unit/l) with subsequent low levels (<1 International unit/l) Serum progesterone levels were reduced to the castrate range in all the patients studied.

The response rate to the combined goserelin and tamoxifen therapy in the 23 patients assessable for response by UICC criteria was 22 per cent (five patients) partial response with a further 22 per cent (five patients) having static disease. Thirteen patients (56 per cent) had progressive disease within 6 months of commencing the goserelin and tamoxifen treatment

Discussion

Goserelin and tamoxifen is a rational drug combination for treating premenopausal patients with advanced breast cancer but it was necessary to confirm that the two drugs were not clinically and endocrinologically antagonistic. Theoretical objections to the combination lay in the fact that tamoxifen alone can produce intermittent peaks of oestradiol in the serum of premenopausal women[4–6]; the effect of tamoxifen therefore might over-ride that of goserelin.

In the premenopausal woman the use of goserelin alone results in the production of serum oestradiol levels equivalent to those after surgical oöphorectomy or in postmenopausal women, although in a few patients recurrent suppressed peaks of oestradiol were noted[3]. In a small clinical study it has been reported that although the LHRH agonist buserelin (3 × 400 μg intranasally daily) in combination with tamoxifen resulted in a response in three of five premenopausal patients with advanced breast cancer, in four of these five patients serum oestradiol peaks occurred[9]. Serum oestradiol peaks were also reported to have occurred in six of ten premenopausal patients with advanced breast cancer during long term therapy with buserelin alone (3 × 400 μg daily), suggesting that oestradiol peaks were due to insufficient LHRH agonist rather than the tamoxifen therapy In a subsequent study this was confirmed castrate levels of oestradiol were reported when the dose of buserelin was increased[10].

In addition to the endocrinological effects of LHRH agonists via pituitary desensitization it has been suggested that these agents may act directly on breast cancers. Miller and colleagues

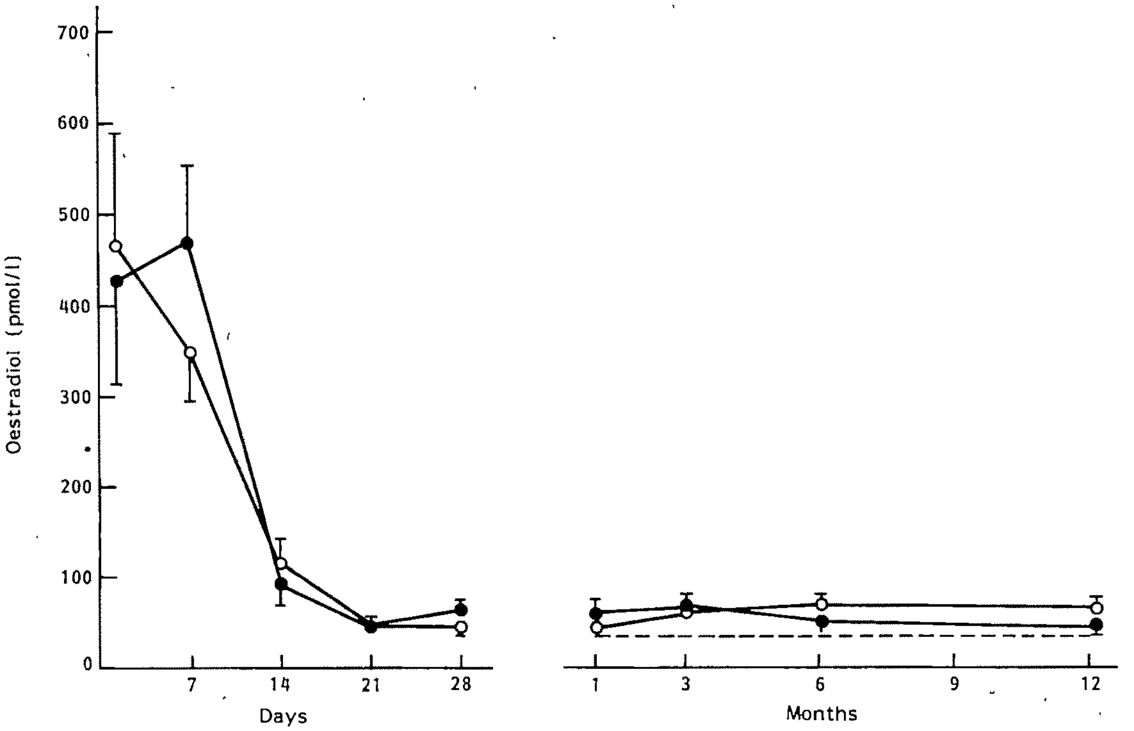

Figure 2 *Mean (s.e.m.) serum oestradiol levels using the old assay in 15 patients treated with goserelin and tamoxifen compared with 24 patients treated with goserelin alone:* ○, *goserelin alone,* ●, *goserelin and tamoxifen,* ---, *castrate level*

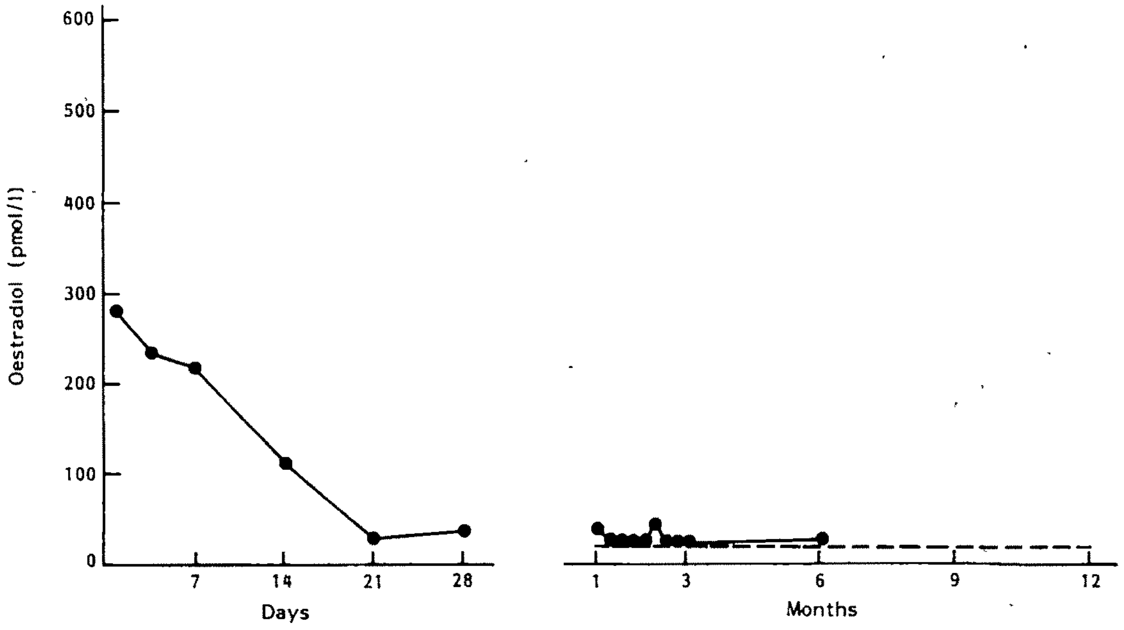

Figure 3 *Mean (s.e.m.) serum oestradiol level using the new assay in 19 patients treated with goserelin and tamoxifen:* ---, *castrate level*

reported a direct inhibitory effect of the LHRH agonist, buserelin, on the growth of the MCF-7 breast cancer cells in culture[11]. A subsequent *in vitro* study reported the effects of buserelin and tamoxifen on the growth of MCF-7 human breast cancer cells[12]. Combined administration of buserelin and tamoxifen was less effective than either buserelin or tamoxifen as single agents in inhibiting the growth stimulation of MCF-7 cells by oestradiol. In view of these findings it was important to establish both that goserelin and tamoxifen were endocrinologically not antagonistic and that a clinical response to the combination was seen in premenopausal patients with advanced breast cancer.

Our results show that goserelin and tamoxifen produce castrate levels of oestradiol and progesterone; no peaks of oestradiol have been recorded in the serum of any of the patients reported in this study. On the contrary, serum FSH concentrations are better suppressed in patients on combination therapy than in those on goserelin alone.

On the combination therapy, five of 23 patients (22 per cent) showed a partial response and a further five (22 per cent) had static disease, both for a minimum duration of 6 months. The reported response rate to goserelin alone was 31 per cent with a further 7 per cent showing static disease for at least 6 months[3]. However comparison of the efficacy of goserelin and tamoxifen *versus* goserelin alone was not the intention of this study. The aims were to establish that, in premenopausal patients with advanced breast cancer, the combination of goserelin and tamoxifen was not endocrinologically antagonistic and could produce clinical response rates similar to surgical oöphorectomy; both of these aims have been confirmed.

Comparison of the clinical efficacy of goserelin and tamoxifen *versus* goserelin alone requires a prospective randomized trial. An international multicentre trial is currently in progress to evaluate whether, in premenopausal women with advanced breast cancer, goserelin and tamoxifen together as an initial therapy will increase the response rate and/or duration of response, compared with goserelin alone as an initial therapy with tamoxifen being added later on tumour progression. This combination may also be suitable for adjuvant therapy but possible long term complications need assessment in that situation.

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Comparison of intracavitary bleomycin and talc for control of pleural effusions secondary to carcinoma of the breast

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In a prospective randomized study, patients with pleural effusions secondary to breast carcinoma were randomly allocated to be treated by pleurodesis using either intracavitary talc or bleomycin. For 25 assessable treatments in 22 patients, recurrence of effusion was observed in 5 of 15 (33 per cent) of the bleomycin group compared with none in the talc group. It is concluded that talc is superior to bleomycin in controlling pleural effusions secondary to breast carcinoma, but bleomycin may have a role in patients unfit for general anaesthesia or with extensive disease elsewhere.

Keywords: Breast cancer, pleural effusion, chemotherapy, pleurodesis

Malignant pleural effusions are commonly seen as a result of metastatic carcinoma of the breast. The mean time between diagnosis of breast carcinoma and development of pleural effusion is more than 3 years, and the mean survival after presentation with effusion is 14 months[1]. Thus effective symptomatic control can significantly improve patients' quality of life. More than half of these patients have other metastases for which they are receiving or will receive systemic therapy[2]. Only rarely can pleural effusion be controlled by systemic treatment alone, and local management provides the most effective method of control. Many agents are in use for pleurodesis, some with cytotoxic properties (mustine, doxorubicin, bleomycin) and others which are sclerosants (talc, tetracycline), with a wide range of efficacy reported[3]. In this unit talc pleurodesis has been previously tested against mustine and tetracycline and found to be superior to both[4,5]. Promising results have been reported using bleomycin, but it has not been directly compared with talc, and for this reason a prospective randomized trial has been conducted.

Patients and methods

Twenty-nine patients with breast carcinoma who had developed radiographically confirmed pleural effusion were entered into the trial No previous local treatment had been given apart from simple aspiration for initial symptomatic relief None had any evidence of non-malignant causes for the effusion Patients were stratified by the presence or absence of other metastases requiring systemic treatment to enable balanced randomization All the patients had the effusion drained to dryness under general anaesthetic and then were allocated randomly to have either a talc pleurodesis or a single intercostal drain inserted. The latter was followed by instillation of bleomycin 1 mg/kg in 50 ml normal saline after a chest radiograph had shown re-expansion of the lung and when the patient could be postured to facilitate distribution of the drug. This was usually performed within 48 h Both the bleomycin and talc treated cases had only one intercostal drain

Assessment of response

Patients were deemed assessable for response to pleurodesis provided they survived for >1 month after the procedure, and they had a repeat chest radiograph at this time The immediate postpleurodesis film was used as a baseline from which to assess subsequent radiographs Success was defined as a continued absence of reaccumulation of pleural fluid on all follow-up radiographs; any reaccumulation was regarded as treatment failure

Results

Twenty-nine patients entered into the study. One patient who was allocated to the bleomycin pleurodesis deteriorated rapidly, the procedure was cancelled, and the patient died a few days later. Another patient who was assigned to talc was unable to have insufflation of the agent because of loculations. After apparently successful pleurodesis two patients in the bleomycin group and three in the talc group survived for <1 month and so were excluded from the analysis. Thus there were 22 assessable patients of whom nine were treated with talc, 12 with bleomycin, and one had talc on one side and bleomycin on the other. Two patients had bilateral bleomycin pleurodeses. In total, ten talc and 15 bleomycin assessable procedures were performed.

Median follow-up was 24 months. During the period of the study 23 of the 29 patients died, and 16 of these survived for <6 months. In these 16 patients, extrapleural disease was encountered in 23 sites compared with nine in the seven patients who survived for >6 months (*Table 1*). Seven patients in the talc and six in the bleomycin group were receiving systemic treatment for disseminated disease. The two groups were similar with regard to age at diagnosis of breast carcinoma and menopausal status, but there were more patients with stage 3 disease in the talc group (*Table 2*). The mean time to development of effusion was shorter in the talc group than in the bleomycin group (46 *versus* 55 months). There was also a longer mean delay between diagnosis of effusion and treatment in the talc group (6·6 *versus* 4·8 months).

In the talc group none of the 10 patients developed evidence of relapse of the effusion compared with 5 of 15 (33 per cent) in the bleomycin group (Fisher exact test $P = 0{\cdot}057$) after a mean follow-up of 9 months. Two patients in the bleomycin group underwent subsequent talc pleurodesis with significant symptomatic improvement in one, but no benefit for the other

Table 1 *Sites of extrapleural disease before pleurodesis in 23 patients who subsequently died*

	Survival	
Site	<6 months (*n*=16)	>6 months (*n*=7)
Cutaneous	8	1
Skeletal	6	3
Lung	5	3
Liver	2	1
Abdomen	1	–
Choroidal	1	–
Central nervous system	–	1
None	3	1

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Table 2 *Characteristics of patients in the two treatment groups*

	Talc ($n=13$)	Bleomycin ($n=16$)
Age (mean)	54·7	53·1
Menopausal status		
Premenopausal	4	6
Postmenopausal	9	10
Stage of disease at presentation		
Stages 1 and 2	5	10
Stage 3	6	3
Unknown	2	3

because of a loculated effusion. The mean survival following pleurodesis in the two groups was identical at 9 months. The procedure was well tolerated and none of the patients developed postoperative complications attributable to it. In fact there was only a minimal degree of postoperative pain, experienced equally by the patients in both groups, and this responded to simple analgesia without need for opiates. The pain was mostly related to the chest drain site. Pleuritic pain was not observed in the talc group, which could be because of the use of non-iodized talc.

Discussion

In this prospective randomized study, talc was shown to be more effective than bleomycin in controlling malignant pleural effusion secondary to breast carcinoma. Although the difference did not quite reach statistical significance, the absence of recurrence in the talc group lends support to the previously reported efficacy of talc in controlling malignant effusions[3,4,6]. To achieve an 80 per cent power of showing the difference at 5 per cent significance level, a further 69 patients would have to be accrued to the trial and this was considered inappropriate. It is likely that, in addition to the inherent effective sclerosant property of talc, its immediate installation after drainage to complete dryness of the pleural cavity contributes to the high rate of success.

Some interesting points emerged from this study. Firstly, 41 per cent of the patients had bilateral and 18·5 per cent contralateral effusions, which suggests mechanisms other than lymphatic obstruction due to direct transthoracic wall lymphatic infiltration[7,8]. Secondly, the median postpleurodesis survival in the group of patients who died was only 2 months (range 0·5 – 16 months) with a median delay of 6 months (range 0·5–48) between diagnosis and treatment. This suggests that for the procedure to be of maximum benefit it should be undertaken as early as possible in the course of the disease. Thirdly, a consideration should be given to the extent of associated tumour burden in order to avoid subjecting patients with very short life expectancy to an unnecessary operation. In this study, there appeared to be evidence of greater tumour load in the patients who survived <6 months compared with those with >6 months survival. The site of extrapleural recurrence did not help us to recognize patients with very short survival. This study differed from previous studies conducted in this unit in that only one intercostal drain was used. It has shown that talc is equally effective as pleural sclerosant with either one or two drains, and the former is preferable both for simplicity and for patient comfort.

Talc remains the most effective agent for controlling malignant pleural effusions in patients who are fit enough for general anaesthesia. The procedure should be undertaken as soon as the effusion is symptomatic and in those patients with minimal disease elsewhere. Patients with pleural effusion and extensive metastases are probably best managed by simple aspiration on the ward as they have a short survival, although present methods of determination of likely length of survival are very imprecise.

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Fibromatosis of the breast

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Ninety-five per cent or more of primary breast neoplasia is of epithelial origin; a small percentage is of mesenchymal origin[1]. Fibromatosis is a locally infiltrative proliferation of well differentiated fibroblasts, which show little atypicality and lack the potential for metastasis, in a collagenous stroma[2,3]. Fibromatosis of the breast accounts for less than 0·2 per cent of all primary breast neoplasms[4,5]. Many of the reports of fibromatosis arising in the breast are limited by lack of follow-up information[6]. We present a case of fibromatosis of the left breast in a 70-year-old woman followed for 17 years.

Case report

A 70-year-old nulliparous Caucasian woman with a past history of fibrocystic change in a left breast biopsy (1964) presented in 1971 with a 2-month history of a 5 × 3 cm nodule in her left breast in the vicinity of the old healed surgical incision. She underwent a hysterectomy for leiomyomata at 50 years of age. There was no family history of breast disease and no history of exogenous hormone therapy. Bilateral mammography demonstrated a suspicious lesion with an infiltrative edge in the left breast highly suggestive of malignancy (*Figure 1*).

Histology of the excised nodule showed a poorly demarcated fibrosarcoma (grade not stated) and because of the histology and mammography report a left simple mastectomy was performed. No residual tumour was demonstrated. Subsequently, 3 and 5 cm diameter nodules were excised from the anterior chest wall in the vicinity of the previous surgery at 12 and 18 months respectively. These were of similar appearance to the initial nodule. A 21-day course of fractionated radiotherapy (3750 cGy) was given to the left anterior chest wall because of the aggressive nature of the lesion.

Five further nodules of similar histological appearance were excised at 6- to 18-month intervals to 1978. They ranged from 1 to 3 cm in diameter and occurred lateral to the previous surgical scars and extended into the left axilla. A 10-year free interval followed to September 1988 when the patient presented with a 3 cm diameter hard fixed nodule in the left axilla which was excised.

At no stage during the 17-year period was there evidence of systemic upset, metastases or lymph node involvement by the process.

Reviewing the histology, including all archival material, similar lesions composed of a population of fibroblasts in interweaving bundles and fascicles in a collagenous stroma (*Figure 2a*) were demonstrated. Areas of variable cellularity were seen, particularly in the later material, which included hyalinized acellular parts. Cytologically there was little atypicality with scanty mitotic figures (fewer than 2 per 10 × 20 field) in all lesions. The periphery of the lesions showed finger-like extensions of the tumour infiltrating surrounding fat and muscle (*Figure 2b*). Trapped and necrotic muscle fibres were present in these areas. Focal lymphocytic infiltrates were present particularly at fat or muscle interfaces. Breast tissue was seen in the early specimen only, with ducts in close proximity to the edge of the infiltrative lesion. The lesion was not related to skin or deep muscle. In retrospect this lesion is best regarded as a benign fibromatosis of the breast.

Discussion

Fibromatosis of the breast is a rare lesion with only 21 cases in the literature[7–15] to 1987. In an extensive review by Wargotz *et al.*[6] 28 further cases were reported. Many of the cases lack follow-up studies to observe the natural history of the process. The patient in this report demonstrates the typical history of these lesions with a potential for multiple recurrences if not adequately excised. The possibility of a well differentiated fibrosarcoma may be difficult to exclude at initial evaluation[7,12,16,17].

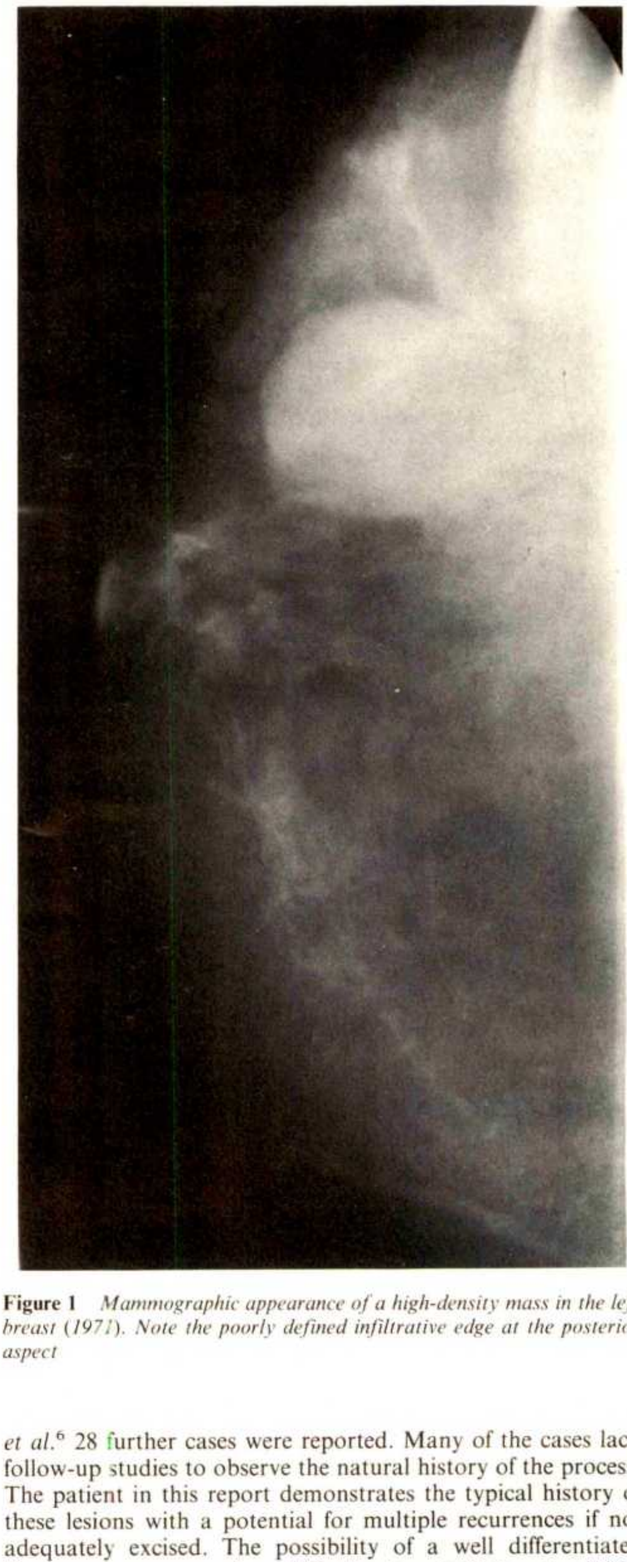

Figure 1 *Mammographic appearance of a high-density mass in the left breast (1971). Note the poorly defined infiltrative edge at the posterior aspect*

Mammograms in eight cases of fibromatosis, including this case, have suggested a malignant lesion[8,10,14,18]. The radiographs show a hyperdense nodule with a poorly defined border and often an infiltrating edge. Fine needle aspiration biopsy for cytology of fibromatosis gives a false positive diagnosis of carcinoma[8]. Lesions of variable cellularity could be subject to sampling error and false-positive diagnoses. Traumatic[19], genetic[14,15] and hormonal[20] factors are proposed as aetiological agents for primary breast fibromatosis. All

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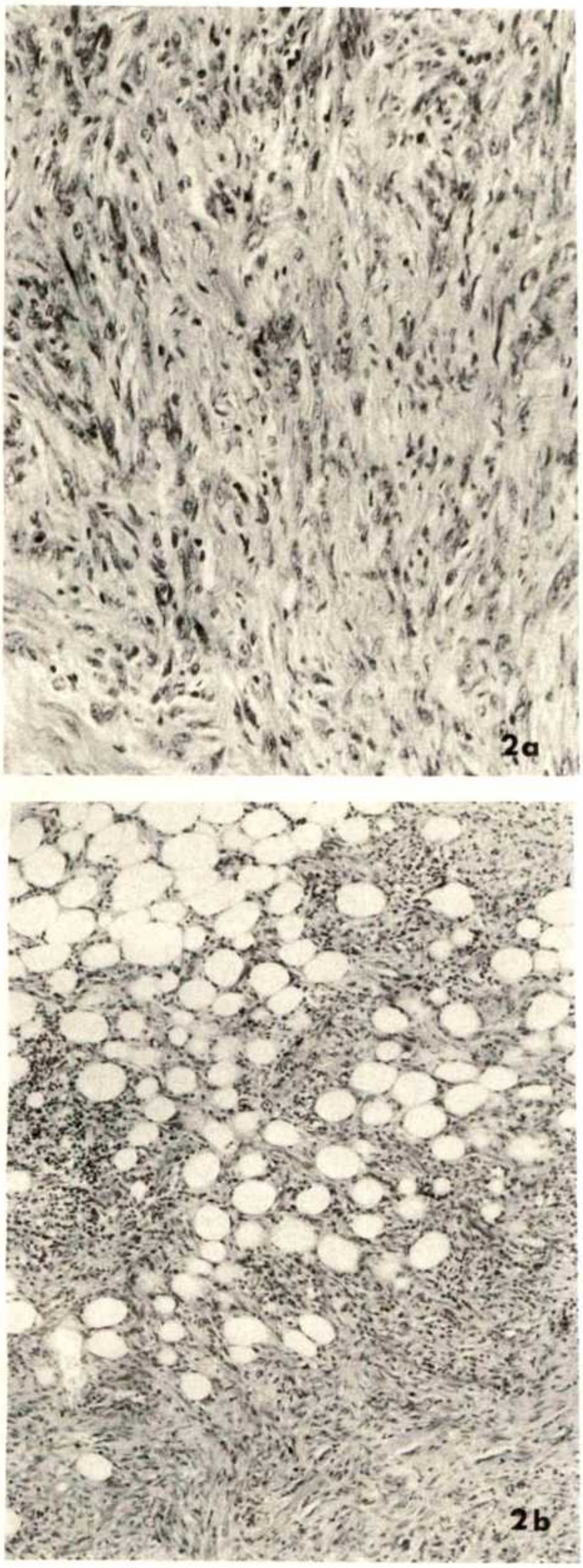

Figure 2 **a** *Representative area of the lesion showing a fascicular arrangement of proliferating fibroblasts* (× *400*). **b** *Edge of the lesion showing infiltration of fat by fibroblasts* (× *400*)

patients have been women[6]. Breast fibromatoses are histologically similar to abdominal fibromatoses or desmoids, which occur at childbearing age and are probably related to stretching of the abdominal musculature by the gravid uterus. The peak incidence of breast fibromatosis is 43 years of age[6] with many occurring in older subjects, suggesting a different pathological process from that of abdominal fibromatosis.

An incisional biopsy in the left breast at the same site, 7 years before presentation of this patient, may have been a contributory factor to the later development of fibromatosis.

Of the series from the Armed Forces Institute of Pathology, 32 per cent had evidence of fibrocystic disease, which was histologically documented in some cases[6]. The 10-year disease-free interval in this case, after repeated recurrences, must reflect on the variable biological behaviour of these processes. The recommended surgical treatment for fibromatosis is wide local excision in view of the often aggressive infiltrative and recurring nature of the process[9,11].

The possibility of fibromatosis of the breast needs to be considered in the population screened in the current national programme[21], especially in those with mammograms and aspirates with false-positive malignant results.

Acknowledgements

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Sample size in fine needle aspiration biopsy

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The weights of biopsy specimens from bovine liver taken for fine needle aspiration cytology (FNAC) by three groups of physicians, were compared. The groups differed from each other in their extent or degree of experience in FNAC. When the physicians used their normal technique, the mean sample weight increased significantly with experience, from 4·6 mg in the least experienced group to 17·2 mg in the group with the longest experience. Thirty-six per cent of the samples taken by the group with the least experience were in the weight class 0–2 mg, whereas no such samples were encountered for the other groups. When all the physicians were advised to use the same, standard technique there were no statistically significant differences in mean sample weight between the groups or in the proportion of samples in class 0–2 mg. Sample weights correlated significantly ($P<0.001$) *with cell counts. This study shows that differences in the technique of FNAC are responsible for differences in sample weights and cell counts, including the number of the acellular samples obtained. This could explain in some part the wide variation in the reported accuracy rates of FNAC.*

Keywords: Fine needle aspiration cytology, cell yield, sample size, technique

The improved awareness of the clinical utility of biopsy for fine needle aspiration biopsy cytology (FNAC) has been responsible for the increase of FNAC performance. This development is partially related to advances in imaging techniques and the refinement of cytological methods. Nuclear magnetic resonance, computed tomography (CT) and sonography have provided improved sensitivity of tumour detection and guided needling to allow tissue sampling from formerly inaccessible sites[1]. In addition to conventional morphological analysis by light microscopy, FNAC samples lend themselves to flow cytometry, tissue culture, biochemical analysis, ultrastructural study, immunological analysis for specific markers, detection and measurement of hormone receptors, and the monitoring of therapy and its effect on malignant tumour cells[2].

However, all these sophisticated methods are inappropriate if cells cannot be aspirated from the target tissue. Studies have shown that up to 43 to 49 per cent of samples for FNAC may be unsatisfactory because of poor yield of representative cells[3,4]. The technique of FNAC has not been studied systematically under controlled conditions. There is no generally accepted technique for FNAC; as a result, each physician tends to use a personal technique. This study shows how this reflects on sample size, explaining some variations in the accuracy of the method[3–10].

Materials and methods

The weights of FNAC biopsy samples taken by three groups of physicians were compared. The groups differed from each other in their experience of FNAC as follows: 'young residents' (five) with a mean of 25 (range 10–40) performed biopsies; 'old residents' (four) with a mean of 75 (range 50–100) biopsies; and 'seniors' (three) with a mean of 750 (range 200–2000) biopsies. Each physician performed 20 FNAC biopsies using his or her usual technique ('free technique'). Thereafter the physicians were required to take ten samples using a 'standardized technique'. In the latter, the tip of the needle was inserted into the target, after which the plunger was pulled back to the 10 ml mark. The physicians were advised to move the needle within the target ten times with a frequency of three strokes per second and with a stroke amplitude of 1·5 cm, suction being maintained throughout. The suction was released before the needle was withdrawn.

Disease-free bovine liver was used as the target tissue. All specimens were taken within 3 h of slaughter. Only the peripheral layer of the liver was used in the experiment to avoid large blood vessels and bile ducts.

A syringe holder (Cameco®, Cameco AG, Täby, Sweden) with a 10 ml disposable syringe was attached to a 22 gauge × 40 mm disposable needle (Terumo Neolus®, Terumo Europe N. V., Leuven, Belgium). A tiny wad of cotton was placed into the hub of each needle to avoid the entry of the specimen into the syringe. The needles with filters were weighed before and after FNAC using a balance (Mettler® Type H 15, E. Mettler, Zurich, Switzerland), accurate to 0·1 mg, standard deviation 0·05 mg). The outer surface of the needle was wiped clean before weighing. The filter did not affect the suction force or its rate of increase, as measured at the needle tip by a pressure sensor (Honeywell Micro Switch® 136 PC 15 G, Honeywell Incorporated, Microswitch Division, Freeport, Illinois, USA) connected to a digital storage oscilloscope (Tektronix® 2210, Tektronix UK Limited, Hoddesdon, UK).

The relationship between weight and cell count of the sample was analysed by microscopical cell counting of specimens with known mass at a magnificiation of × 100. For this, the specimens were fixed in 50 per cent ethanol, collected on a Millipore® (Millipore S. A., Mollsheim, France) filter, and stained with Papanicolaou's stain. For each specimen, the cell count of 30 fields was calculated. The total cell count was obtained by multiplying the mean value per view field by 1.0×10^4, which was the ratio between the area of the Millipore filter and that of the view field.

Lilliefors modification[11] of the Kolmogorov–Smirnov test was used to analyse the normality of the mass distribution curves. Means were compared using Student's t test for unpaired samples, and proportions by using the χ^2 test.

Results

With the free technique, the mass distributions were positively skewed and therefore subjected to square root transformation to obtain better normal probability plots before comparing the mean sample weights obtained by the three groups (*Table 1*). After transformation back to the original scale, the mean (95 per cent confidence interval) weight of the specimens taken by seniors was 17·2 mg (15·1–19·5 mg), by old residents 10·5 mg (9·2–11·8 mg) and by young residents 4·6 mg (3·6–5·8 mg; *Figure 1*). The differences were statistically highly significant (*Table 1*). When the standardized technique was used the corresponding values were: seniors, 10·9 mg (9·1–12·7 mg); old residents, 11·6 mg (10·1–13·0 mg); young residents, 10·2 mg (8·2–12·2 mg; *Figure 1*). There was no statistically significant difference between the groups (*Table 1*).

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Table 1 *Comparison between the mean sample weights obtained by three groups of physicians*

	Technique	Difference between means	95% confidence interval for difference between means	Student's *t* value	d.f.	*P*
'Seniors' *versus* 'old residents'	'free'	0·9	0·6 to 1·2	5·6	138	<0·001
'Seniors' *versus* 'young residents'	'free'	2·0	1·6 to 2·4	10·2	158	<0·001
'Old residents' *versus* 'young residents'	'free'	1·1	0·7 to 1·4	6·3	178	<0·001
'Seniors' *versus* 'old residents'	'standard'	−0·7	−2·9 to 1·5	−0·6	68	0·52
'Seniors' *versus* 'young residents'	'standard'	0·7	−1·9 to 3·2	0·4	78	0·66
'Old residents' *versus* 'young residents'	'standard'	1·4	−1·6 to 4·3	1·1	88	0·29

Values obtained by a 'standardized technique' are in original scale; values obtained by a 'free technique' have been subjected to square root transformation

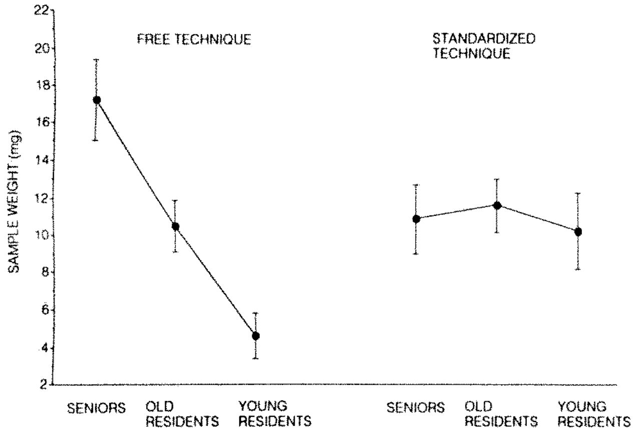

Figure 1 *Mean sample weights with 95 per cent confidence intervals obtained by three groups of physicians using a 'free technique' and a 'standardized technique'*

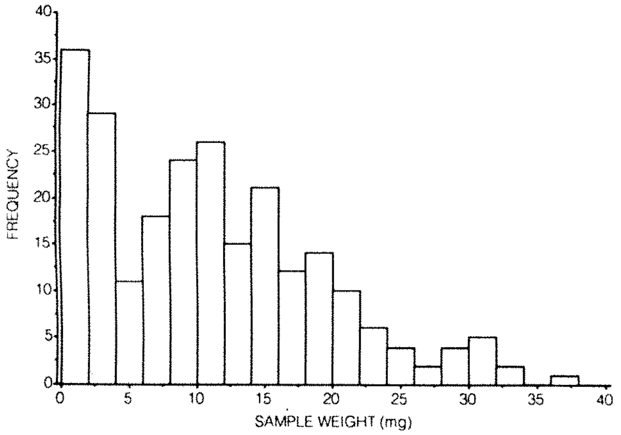

Figure 2 *Frequency distribution histogram of all sample weights obtained by a 'free technique'*

Figure 2 shows the frequency distribution histogram of all samples taken with the free technique. Division of the range of masses into 20 classes of equal size determined 0–2 mg as the lowest weight class. When the free technique was used, 36 per cent of samples (36 of 100) taken by young residents fell into this class, whereas none of the samples taken by old residents (80) or seniors (60) did so. This intergroup difference was statistically significant ($P<0{\cdot}001$). With the standardized technique (not shown) there was no statistically significant difference between the groups, the corresponding proportions being 8·0 per cent (four of 50), 2·5 per cent (one of 40) and 3·3 per cent (one of 30); $\chi^2=1{\cdot}48$, d.f. $=2$, $P=0{\cdot}48$.

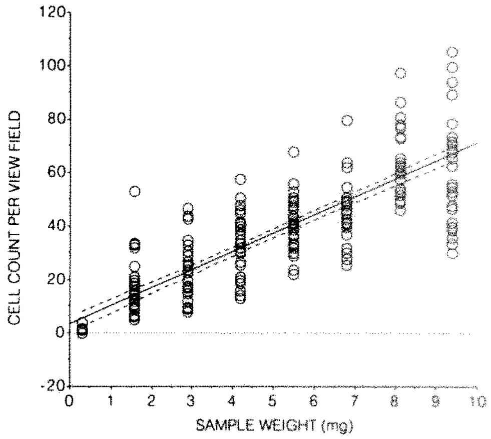

Figure 3 *Correlation of sample weight with cell count per view field at a magnification* ×*100* ($r=0{\cdot}85$, $n=240$, $P<0{\cdot}001$)*. Regression line* $y=6{\cdot}8x+3{\cdot}2$ *with a 95 per cent confidence interval*

Figure 3 shows the statistically significant ($P<0{\cdot}001$) correlation between sample mass and the count of liver cells per view field.

Discussion

In clinical studies the accuracy values of FNAC have varied considerably, e.g. in cancer of the breast from about 50 per cent to over 95 per cent[3–10]. Part of this fluctuation can be explained by differences in patient selection[3,4,6,8,10], or in the selection of samples for the preparation of smears[3,4,8], or in the selection of smears for the calculation of accuracy values[3,4,8]. The equipment used in FNAC can be chosen from a variety of needles with different cutting tips, bevels and calibres[9,12–15], from a variety of syringes[4,8,14] and syringe holders[2,3,10,14,16]. For some physicians the syringe holder is omitted[8,9,12]. There are also differences in aspiration technique. Each physician appears to have evolved a favourite method which he terms FNAC. *Figure 2* shows how free choice in the technique of FNAC reflects on sample size when uniform equipment is used.

With the free technique the experienced physicians obtained significantly larger samples (*Figure 1*) and none of the samples was in the smallest weight class, 0–2 mg, whereas 36 per cent of the samples taken by young residents were under 2 mg in weight. This has important clinical consequences as samples containing few or no cells (acellular) appear in this class. When all physicians participating in the study used the standardized technique there were no differences between the three groups (*Figure 1*), suggesting that the major factor causing the intergroup difference with the free technique was the technical procedure itself (e.g. number, amplitude and frequency of strokes, force of suction). As there is a linear dependence between sample weight and cell count (*Figure 3*) the results obtained can also be applied to cell counts. Thus, the cell count of a sample is determined by the target tissue[12] and by the FNAC technique used. With a set target the only way to enhance cell yield is to optimise the FNAC technique. Although cytopathological quality is subjective it seems that an increase in sample size also leads to better sample quality[13,15].

Regarding FNAC in mammary carcinoma, Dixon *et al.*[5,6] noticed that when there were several aspirators, both junior and senior members of the clinic, the sensitivity of the method was only 59–66 per cent and 19–27 per cent of smears were acellular. When this policy was changed so that all FNACs were performed by only one surgeon using a standard technique the sensitivity increased to 99 per cent and only 1 per cent of samples were acellular. The authors emphasized that a major factor determining the quality of specimens was the experience of the aspirator. The present study, however, shows that the sample quality and the number of unsatisfactory specimens is not only dependent on the experience of the aspirator but also on the technique used. In addition, the high sensitivity noted by Dixon *et al.* can be partly related to better targeting by an experienced operator; tactile sense and augmenting the probability of sampling the lesion by the number and direction of needle passes around the suspect area. Finally, additional aspirations will be made until a macroscopically sufficient sample is obtained.

The various recommendations on how FNAC should be carried out are contradictory and indefinite. Furnival *et al.*[8] reported that the rate of technically unsatisfactory aspirates was 24·8 per cent when the needle was gently moved within the tumour and when suction was maintained as the needle was withdrawn. If the needle was moved more actively and the suction released before withdrawing the needle, the frequency of inadequate samples was decreased to 6 per cent. Duguid *et al.*[14] found that failure to maintain suction when the needle is traversing the lesion leads to poorly cellular samples, and that a better cell yield is obtained when suction is maintained during removal of the needle from the target. These authors also observed that wetting the inside of the needle with saline–heparin solution definitely improves the cellularity of smears. According to Zajicek[16], the syringe and the needle must be absolutely dry when FNAC is performed. Although the number of needle passes within the tumour ranges from 2 to 15 in different reports[4,5,7,14], Hartley *et al.*[12] concluded that there appears to be no advantage in exceeding ten passes or in using needles larger than 21 Fr. Andriole *et al.*[13] noted an improvement in sample size and quality with increasing needle bore and obtained the best results with 18 Fr needles.

One explanation for these different observations might be found in the wide range of variables in the technique of FNAC, including suction (force, duration and rate of increase), needle movement (number, frequency and amplitude of passes, angle between the passes, acceleration of movement), needle (size, content, tip configuration) and target tissue. The simultaneous control and measurement of all these variables is difficult or even impossible with the manual equipment used in FNAC. Still, the development of an optimal technique would appear to require an investigation of the effects of each variable separately. So far, no such studies have been reported.

In conclusion, this study demonstrates that the best way to improve sample quality and to avoid acellular samples is improvement of the technique of FNAC. However, the technique has not been studied systematically under controlled conditions and the actual mechanism of cell sampling that occurs during the aspiration biopsy is not clear. As a result there are no generally accepted guidelines on how FNAC should be performed.

Acknowledgements

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Short note

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Role of fine needle aspiration cytology and computed tomography in the diagnosis of parotid swellings

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Operations on the parotid gland present a considerable surgical challenge because the anatomy is delicate and the pathology diverse[1]. Formal parotidectomy has become the preferred treatment for space-occupying lesions[2]; this approach has evolved because pleomorphic adenoma is the commonest lesion. This operation can be technically demanding and the residual disabilities are serious in a significant number of patients. Facial nerve palsy is the single greatest problem, and can be temporary (11–82 per cent) or permanent (0–17 per cent)[3]. Masses of benign origin on the other hand require only enucleation and this has a lower morbidity[4]. Therefore, an accurate preoperative diagnosis would allow less radical surgery in some patients and should reduce complications.

Patients and methods

The case notes of 84 patients presenting with a lump in the parotid region over an 8-year period (1981–88) have been reviewed. Following clinical diagnosis of a lump in or related to the parotid gland two additional diagnostic methods have been used.

Forty-four patients (34 men) were investigated by fine needle aspiration cytology (FNAC) using a standard technique. The age range was 17–81 years. The preoperative cytological diagnosis was compared with the final histopathological one after examination of the surgical specimen. In addition, the last 18 patients had a computed tomographic (CT) scan of the parotid region.

Results

The results and accuracy of fine needle aspiration are shown in *Table 1*. The accuracy was 100 per cent with pleomorphic adenoma and 75 per cent with adenolymphoma with no false positive or false negative diagnoses of malignancy. Follow-up ranged from 4 to 96 months with a mean of 30, and there have been no local recurrences to date. Three patients had tuberculosis of the parotid gland diagnosed by FNAC and were treated medically. In all three, FNAC showed the typical appearances of a granuloma, and culture of the aspirate grew mycobacteria.

All CT scans have shown the presence of a tumour in the superficial part of the parotid (*Figure 1*) with deep extension seen in three (*Figure 2*).

Table 1

	Diagnostic	Inadequate	Accuracy (%)
Pleomorphic adenoma ($n=26$)	26	0	100
Adenolymphoma ($n=8$)	6	2	75
Carcinoma ($n=4$)	4	0	100
Others ($n=6$)	5	1	–

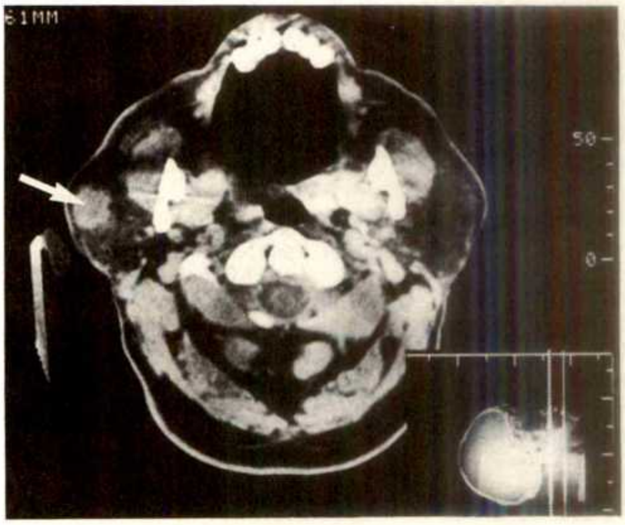

Figure 1 *Computed tomographic scan showing accurate delineation of a mass in the right superficial parotid (arrow)*

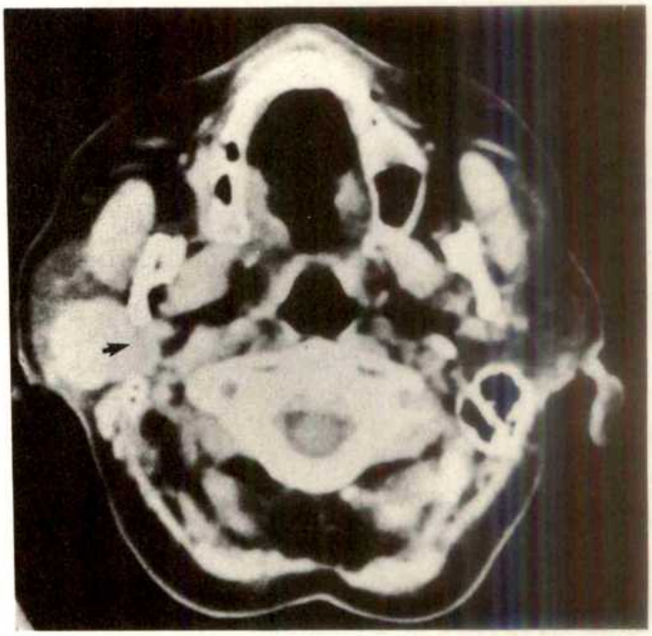

Figure 2 *Computed tomographic scan showing a superficial lesion with clear demonstration of deep extension into the parotid (arrow)*

Discussion

FNAC is a simple, inexpensive method for obtaining a tissue diagnosis and numerous reports in the literature demonstrate its accuracy[5,6]. Complications of FNAC of the parotid are infrequent, minor and transient. Haematoma and superficial infection are rarely seen and did not occur in this series. Dissemination of tumour cells or cell clusters via the needle track, efferent lymphatics or blood vessels with resultant

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extension of the neoplastic growth is a theoretical risk, but no published series, including the present study, have demonstrated this when a fine needle (18–22 gauge) is used with a single skin pass technique.

Eneroth *et al.*[7] and Lindberg and Akerman[8] in a series of 1860 salivary gland tumours had no recurrences following FNAC. Engzell *et al.*[9], in a retrospective analysis of 157 pleomorphic adenomas with a 10-year follow up, demonstrated three tumour recurrences following FNAC; two of these, however, were associated with incomplete excision of the primary tumour.

In the occasional case reports of growth along needle tracks, either a large calibre Vim-Silverman needle or multiple skin passes with a fine needle were used. However, follow-up in this series is too short as yet to be certain that there is no risk of implantation. A recent report of tumour implantation after FNAC of a colonic hepatic metastasis gave no details of the aspiration technique[10].

CT will show lesions extending outside an organ or arising in adjacent structures. This is a particular advantage with the parotid gland since it is a small structure and even primary lesions may be predominantly extraglandular[11]. CT provides precise anatomical detail showing the exact location of a mass within the gland. Pleomorphic adenomas are usually seen as a sharply defined mass with smooth borders (*Figure 1*). Furthermore, it is of great value to ascertain the size and extent of involvement of the gland, which is accurately demonstrated by this technique (*Figure 2*). The surgeon is thereby forewarned of the extent of the operation and the higher risks involved.

These two investigations will provide an accurate preoperative diagnosis of the histological type and anatomical site of a parotid mass, enabling the surgeon to select those tumours, such as adenolymphoma, which require local excision only, and to avoid operative intervention for inflammatory or secondary neoplastic conditions. This approach should reduce the complications of unnecessarily extensive procedures.

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Management of high grade parotid carcinomas

Thirty-four patients admitted to the Bristol Royal Infirmary during the 20-year period 1966–85 and diagnosed as suffering from high grade parotid carcinoma were studied. The male:female ratio was 2·4:1, with a mean age at presentation of 68 years. Facial swelling was present in all patients with a mean duration of 9·9 months before treatment. Pain, deep fixation, facial nerve involvement, ulceration and distal metastases were all associated with a poor prognosis. Diagnosis was made either at operation or by fine needle biopsy. All 34 patients received radiotherapy. Fourteen patients (41 per cent) underwent a definitive surgical procedure. The local recurrence rates for the non-surgical and surgically treated groups were 30 per cent (six patients) and 36 per cent (five patients) respectively; twelve patients (60 per cent) in the non-surgical group developed distant metastases as opposed to six patients (43 per cent) in the surgical group. Both local and distant recurrent disease are indicators of poor prognosis, with only one patient alive at 104 months. Seven patients (21 per cent) remain recurrence free. Definitive surgery, combined with radiotherapy, improved survival in those with amenable localized disease.

Keywords: Carcinoma of the parotid, fine needle aspiration cytology

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Parotid tumours account for 73 per cent of all salivary gland neoplasms, of which 15 per cent are malignant[1]. High grade parotid carcinomas include poorly differentiated adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma and carcinoma arising in pleomorphic adenomas[2]. This group of tumours is uncommon, comprising less than 7 per cent of all parotid neoplasms[1]. Their diagnosis and treatment remains controversial. Although the benefits of postoperative radiation therapy have been widely accepted[3–8], the initial diagnostic procedure together with the timing and extent of surgical excision is uncertain.

Since 1966, 34 patients with high grade parotid carcinoma have been treated at the Bristol Royal Infirmary. Of these, 14 received combined surgery and radiotherapy, whereas in 20, after an initial diagnostic biopsy, radiotherapy alone was employed. The purpose of this study is a retrospective comparison between the two treatment groups with respect to recurrent disease and subsequent survival.

Patients and methods

All patients diagnosed at the Bristol Royal Infirmary as suffering from high grade parotid carcinoma during a 20-year period, 1966–85, were identified from hospital records (diagnostic index and pathology files). In each case the diagnosis was confirmed by review of the original histological and cytological slides. Review of the histology revealed nine poorly differentiated adenocarcinomas, ten undifferentiated tumours, two carcinomas arising in pleomorphic adenomas, and one poorly differentiated squamous cell carcinoma. Cytological review added a further five poorly differentiated adenocarcinomas and seven undifferentiated tumours. All tumour types were grouped together as high grade parotid carcinomas for the purpose of data analysis.

Results

A total of 34 patients (24 men, 10 women, mean age 68·0 years, range 41–87 years) were identified. Of these, 16 of the tumours were on the left and 18 on the right.

Presenting symptoms (Table 1)

All patients presented with facial swelling (mean duration 9·9 months, range 2–48 months) and 13 complained of pain (mean duration 6·7 months, range 2–18 months). Thirty tumours demonstrated deep fixation, 15 lymph node involvement, and in ten 7th nerve palsy was evident. Distant metastases were present in seven and skin ulceration in five.

Initial diagnostic procedure

Parotidectomy without biopsy was performed in eight patients (superficial parotidectomy in six and total parotidectomy in two), whereas an open incision biopsy procedure was the diagnostic method in 14. Fine needle aspiration biopsy cytology was performed in 12.

Definitive surgical procedure

Of the 26 patients receiving initial tumour biopsy, six subsequently underwent further definitive surgery (three total parotidectomies, two superficial parotidectomies and one local excision). All 34 patients received radiotherapy; in addition, five patients accepted chemotherapy.

Survival analysis (Table 2)

To date, five patients are alive (mean 73·8 months, range 10–156 months) and 29 dead (mean 15 months, range 1–60 months). Seven patients have remained totally recurrence free, and four of these are still alive (mean 66·3 months, range 10–156 months). Three deaths were due to unrelated pathology (mean 26 months, range 10–35 months). Local recurrence occurred in eleven patients of whom only one is still alive at 104 months. The mean survival in this group was 18 months (range 6–29 months). Distant recurrence developed in 18 patients, all of whom died (mean 16·8 months, range 1–60 months).

Survival as function of treatment (Table 3)

Radiotherapy alone following initial biopsy procedure. In 20 patients there was no definitive surgical excision. Two remained recurrence free, one of whom is still alive at 58 months; the other died of unrelated disease at 10 months. Local recurrence occurred in six patients at a mean of 8·5 months (range 2–19 months). All in this group are now dead (mean 16·8 months, range 1–38 months). Distant recurrence occurred in 12 patients,

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Table 1 *Prognostic indicators*

		Outcome					
		Alive			Dead		
	Total patient number	*n*	Mean (months)	Range (months)	*n*	Mean (months)	Range (months)
Pain							
Yes	13	0	—	—	13	12·3	1–33
No	21	5	73·8	10–156	16	19·6	2–60
Deep fixation							
Yes	30	5	73.8	10–156	25	15·9	2–60
No	4	0	—	—	4	18·9	1–33
Ulceration							
Yes	5	0	—	—	5	13·6	4–23
No	29	5	73·8	10–156	24	17·1	1–60
Facial nerve involvement							
Yes	10	0	—	—	10	17·6	6–60
No	24	5	73·8	10–156	19	15·6	1–35
Distant metastases							
Yes	7	1	10·0	—	6	5·3	2–12
No	27	4	89·8	41–156	23	19·2	1–60
Lymph node involvement							
Yes	15	2	57·0	10–104	13	12·9	2–27
No	19	3	85·0	41–156	16	19·3	1–60

Table 2 *Prognosis as a function of recurrent disease*

		Outcome					
		Alive			Dead		
Recurrence type	Total patient number	*n*	Mean (months)	Range (months)	*n*	Mean (months)	Range (months)
None	7	4	66·3	10–156	3	26·0	10–35
Local	11*	1	104	—	10	18·0	6–29
Distant	18*	0	—	—	18	16·8	1–60

* Includes patients with local and distant recurrence

Table 3 *Survival as a function of treatment*

			Outcome					
			Alive			Dead		
Operation	Recurrence type	Total patient number	*n*	Mean (months)	Range (months)	*n*	Mean (months)	Range (months)
None	None	2	1	58·0	—	1	10·0	—
($n=20$)	Local	6	0	—	—	6	16·8	1–38
	Distant	12	0	—	—	12	16·4	1–60
Local excision	None	0	0	—	—	0	—	—
($n=1$)	Local	1*	0	—	—	1	23·0	—
	Distant	1*	0	—	—	1	23·0	—
Superficial parotidectomy	None	4	2	130	104–156	2	34·0	33–35
($n=8$)	Local	2	1	104	—	1	10·0	—
	Distant	2	0	—	—	2	17·0	14–20
Total parotidectomy	None	1	1	10·0	—	0	—	—
($n=5$)	Local	2*	0	—	—	2	15·0	3–27
	Distant	3*	0	—	—	3	14·0	9–27

* Includes patients with local and distant recurrence

and all have subsequently died (mean 16·4 months, range 1–60 months).

Combined surgical excision and radiotherapy. Of these 14 patients, five remained recurrence free. Three are alive (mean 90 months, range 10–156 months) and two have died of unrelated disease (mean 34 months, range 33–35 months). Local recurrence developed in five patients (mean 14·6 months, range 1–60 months), four of whom are dead (mean 17·3 months, range 3–27 months), with a sole survivor at 104 months. Of the six patients who developed distant metastases, all died (mean 16·5 months, range 9–27 months).

A detailed analysis of surgical procedure related to recurrence rate and subsequent survival is given in *Table 3*. In addition to the above treatment, five patients received adjuvant chemotherapy. All of these are dead with a mean survival of

16·6 months (range 6–27 months). The mean survival of the non-chemotherapy patients is 16·25 months (range 1–60 months).

Discussion

Salivary tumours are most common in the parotid gland; consequently the majority of malignant salivary tumours are in this gland. Although surgical excision, with or without radiotherapy, remains the standard treatment for benign and well differentiated malignant parotid neoplasms, uncertainty exists regarding the treatment of high grade carcinomas. During the past decade there has been an inclination towards treatment by radiotherapy, after diagnosis by fine needle aspiration or an alternative biopsy technique[9].

Although several studies have reported the efficacy of surgery and radiotherapy in controlling local disease[3–5,7,8,10,11], its potential for prolonging life expectancy is unsure. Since all our patients received radiotherapy, the effect of surgery on the recurrence and survival rates can be assessed.

Some groups advocate radical surgery in all cases of parotid malignancy[5,12–14], although survival rates have not been improved[15,16]. A more conservative operative approach combined with radiotherapy is an alternative option[4,5,7,16].

Management of high grade parotid carcinomas is complicated by the paucity of cases and the relative lack of comparative data. A widely reported 5-year survival rate is 25 per cent, despite an aggressive surgical approach[17]. Since the morbidity following radical parotidectomy is itself high[5,17], a less extensive surgical approach is preferable, provided recurrence and mortality rates remain unchanged. At the Bristol Royal Infirmary, fine needle aspiration biopsy remains the investigation of choice in the diagnosis of malignant parotid lesions[18]. This investigation is very unlikely to result in tumour seeding[19]; in the present study no increased incidence of local recurrence is noted following incisional or needle biopsy, when compared with a definitive surgical approach.

Both local and distant recurrences are associated with a poor prognosis (*Table 2*). Of the 18 patients developing metastatic disease, all are now dead at a mean of 16·4 months and 16·5 months for the non-operative and operative groups respectively. Only one patient with local recurrence is still alive.

To date, seven patients (21 per cent) are free of recurrence. Recurrence of these high grade carcinomas in the parotid therefore carries a disastrous prognosis. These lesions are usually highly infiltrative, extending well beyond the primary site, and regardless of radical secondary surgery prognosis remains poor[8,20]. Definitive primary management is clearly important and should be tailored to the clinical state. Indicators of poor prognosis include pain, deep fixation, superficial ulceration, facial nerve involvement and distal metastases (*Table 1*).

From our study, it seems that definitive surgery is unlikely to influence survival and a more conservative approach would appear to be preferable. However, in the absence of the above prognostic indicators, surgical intervention can increase the mean survival, primarily owing to its effect in lowering the probability of developing locally recurrent disease (*Table 3*).

Despite the relatively large number of patients available for this study, the variety of different treatment regimens renders comparison imprecise. It is our impression that patients with localized or minimally invasive disease who are otherwise fit for surgery should receive it. Although the local recurrence rates remain unaffected, survival appears to be improved. We cannot confirm the view that radical as opposed to superficial parotidectomy is preferable, except perhaps for deep lobe involvement.

Since the results for advanced disease are so poor, a less radical approach, consisting of radiotherapy after fine needle aspiration biopsy diagnosis, may be a more rational treatment.

The value of fine needle aspiration biopsy in the early diagnosis of parotid neoplasms is emphasized. Early diagnosis of all parotid lesions is essential if the results of surgical management of this aggressive tumour are to be improved. The mean time delay of 9·9 months between the appearance of facial swelling and the diagnosis in the present series can surely be improved.

The importance of early diagnosis in all parotid swellings needs strong emphasis and swift referral to a specialist centre for salivary tumours is desirable. Fine needle aspiration biopsy may be performed very simply and definitive treatment may be planned according to the disease staging. The sensitivity of aspiration cytology for salivary carcinoma is high. For locally advanced disease with evidence of metastases at presentation, palliative radiotherapy alone after some form of biopsy is sufficient; no obvious advantage is to be gained from a major surgical procedure. It is suggested that management should be designed to match the stage of disease presentation: early diagnosis appears to offer the best chance of improving survival.

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Medullary carcinoma of the thyroid: management of persistent hypercalcitonaemia utilizing [^{99m}Tc](v)dimercaptosuccinic acid scintigraphy

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Whole body scintigraphy with [^{99m}Tc](v)dimercaptosuccinic acid (pentavalent DMSA) was performed in seven patients with histologically confirmed medullary carcinoma of the thyroid (MCT). Six of these patients had undergone previous thyroid resections for MCT and, although asymptomatic at the time of pentavalent DMSA scintigraphy, had persistent and serial elevations in their plasma calcitonin levels. One additional patient was scanned before and after total thyroidectomy for MCT. The pentavalent DMSA scintigram demonstrated either local neck recurrence (three patients) or distant metastases (two patients) in five of the six asymptomatic patients. In one asymptomatic patient only equivocal neck uptake was demonstrated. Since he had only minimal calcitonin elevations, repeat neck exploration was not performed. The one patient studied before thyroid resection for MCT demonstrated neck uptake before, but not after, total thyroidectomy. The results of the scintigrams had significant impact on patient care and resulted in neck re-exploration (three patients), neck biopsy (one patient), and lumbar spine biopsy and subsequent radiotherapy (one patient). These data demonstrate pentavalent DMSA to be a sensitive localizing agent in the evaluation of asymptomatic MCT patients with hypercalcitonaemia. Accurate targeting of treatment may be shown in due course to have a beneficial impact on survival.

Keywords: Medullary carcinoma of the thyroid, [^{99m}Tc](v)dimercaptosuccinic acid, hypercalcitonaemia, Sipple syndrome

Medullary carcinoma of the thyroid (MCT) was first described as a distinct clinical entity by Hazard *et al.*[1] in 1958. This solid tumour behaved as an intermediate thyroid malignancy in terms of its aggressiveness, with the propensity for local lymph node metastasis, distant metastasis and an indolent course. The familial occurrence of thyroid carcinoma in association with phaeochromocytoma was subsequently recognized by Sipple and the multiple endocrine neoplasia (MEN 2a) syndrome was described[2]. MCT has been of particular oncological interest because this tumour, which arises from the parafollicular cells, secretes the specific tumour marker calcitonin. Calcitonin screening in MEN kindreds has resulted in the early diagnosis and treatment of MCT in affected family members[3].

The surgical approach to patients with MCT is generally a total thyroidectomy[4–6] and removal of nodes in the primary lymphatic drainage area. Although most patients demonstrate a marked diminution in their postoperative calcitonin levels, a significant subset of patients have persistent postoperative hypercalcitonaemia. Faced with the clinical dilemma of recommending therapy for these asymptomatic post-thyroidectomy patients who had persistent and serial elevations in their calcitonin levels, we sought the use of radiopharmaceuticals that were reported to have high sensitivity and specificity for MCT. Initial enthusiasm for iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG)[7–9] was tempered by a series of articles reporting equivocal results[10–13]. Therefore we used a modified isotope complex, pentavalent DMSA ([^{99m}Tc](v)dimercaptosuccinic acid), which has been recently reported by three groups to have encouraging sensitivity for MCT[14–16]. In this paper we describe the efficacy and clinical utility of [^{99m}Tc](v)DMSA as a localizing agent in six asymptomatic patients with persistent hypercalcaemia after thyroid resection for MCT. An additional case in which we performed scintigraphy both before and after total thyroidectomy for MCT is also presented.

Patients and methods

Seven patients with histologically confirmed MCT were selected for study (*Table 1*). Six of the patients were asymptomatic, but had persistent and serial elevations in their plasma calcitonin levels after undergoing either total thyroidectomy (five patients) or thyroid lobectomy (one patient) (*Figure 1*). One patient had MCT diagnosed preoperatively by a fine needle aspirate of a thyroid nodule. All patients underwent pentavalent DMSA scintigraphy in an attempt to localize their source of calcitonin production.

[^{99m}Tc](v)DMSA was prepared according to the method of Sampson[17]. Briefly, 4 mg DMSA, 120 mg dextrose and 5 mg sodium bicarbonate were added to a standard vial of DMSA (Amersham International plc, Buckinghamshire, UK) and the mixture was dissolved in 0·4 ml of 7 per cent w/v sodium bicarbonate solution. About 600 MBq [^{99m}Tc] pertechnetate was made up to 2·5 ml with normal saline and added to 0·1 ml of the DMSA solution in a mixing vial. The mixture was then passed through a 0·22 mm filter and 370 MBq of the filtered solution were injected within 1 h of preparation. Thin layer chromatography was used to assess the production of pentavalent DMSA.

Blood pool images were acquired 10 min after injection and whole-body planar scintigraphy was performed 2 h later using a General Electric Maxicamera 400 T (IGE Medical Systems Ltd., Slough, UK) fitted with a low-energy high-resolution collimator and interfaced to a computer with data display facilities. 550 000 counts were obtained per image. The appearance of isolated photon-abundant areas (hot spots) in the 2-h scintigrams were taken to indicate the presence of metastatic MCT.

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Calcitonin was measured by radioimmunoassay in rapidly frozen plasma samples. The normal range is <0·08 ng/ml with an intra- and inter-assay variation of 9 and 13 per cent, respectively.

All pathological material was reviewed by a single pathologist and the diagnosis of MCT was verified in every case.

Case reports

The following case reports are summarised in *Table 1*.

Case 1. A 53-year-old woman underwent left total thyroid lobectomy for a painless left neck mass. The specimen contained MCT with extensive capsular and vascular invasion. The right lobe and isthmus were removed 2 weeks later, but there was no evidence of MCT or C cell hyperplasia in the specimen. Her initial postoperative calcitonin level of 0·1 ng/ml was monitored and had risen to 0·28 ng/ml 3 years later. It then rose steeply over the next year to a peak of 2·13 ng/ml. She remained asymptomatic. A pentavalent DMSA scintigram demonstrated uptake in her lumbar spine (*Figure 1a*). A computed tomography (CT) scan confirmed a lytic lesion in the body of L3 (*Figure 1b*) and she rapidly developed diarrhoea and back pain. A bone biopsy confirmed metastatic MCT and whilst undergoing palliative radiotherapy the affected lumbar vertebra started to collapse requiring internal fixation. The calcitonin level has ceased to rise and is currently stable at 2·01 ng/ml.

Case 2. A 48-year-old woman underwent left thyroid lobectomy and a frozen section was highly suggestive of MCT. A total thyroidectomy was performed. A single focus of MCT was verified in the left thyroid lobe. A postoperative thyroid scan demonstrated no residual thyroid tissue. She remained asymptomatic but serial calcitonin levels began to rise 5 years later to a peak of 1·13 ng/ml 6 years after operation. A pentavalent DMSA scintigram demonstrated increased uptake in the anterior neck (*Figure 2*). In spite of the fact that the tumour was evident on neither clinical examination nor CT

Table 1 *Profiles of patients with medullary carcinoma of the thyroid*

Patient	Sex	Age at diagnosis	Sporadic *versus* familial	Initial procedure	Postoperative calcitonin (ng/ml)	Serial calcitonin peak (ng/ml)	Years since diagnosis	Uptake of [^{99m}Tc](v) dimercapto-succinic acid	Procedure	Finding
1	F	53	S	Total thyroidectomy	0·1*	2·13	4	Lumbar spine	Bone biopsy	Metastatic MCT
2	F	48	S	Total thyroidectomy	0·37	1·13	6	Anterior neck	Neck re-exploration	Metastatic MCT
3	M	20	S	Total thyroidectomy, modified radical neck, left pneumonectomy	46·7	43·0	3	Mediastinum	Computed tomography scan	Unresectable
4	F	42	S	Needle biopsy	1·89† 0·05‡	NA	NA	Bilateral neck, ?Thymus	Total thyroidectomy, thymectomy	MCT left thyroid lobe, Normal thymus
5	F	45	S	Right thyroid lobectomy	0·19	0.20	2	Right anterior neck	Neck re-exploration	Metastatic MCT
6	M	45	F	Left thyroid lobectomy, modified radical neck	0·76	2·6	24	Right anterior neck	Neck re-exploration	Pending
7	M	20	F	Total thyroidectomy	0·1	0·13	8	Equivocal uptake anterior neck	Plan serial evaluations	

NA, not applicable; MCT, medullary carcinoma of the thyroid. * Normal <0·08 ng/ml; † prethyroidectomy; ‡ post-thyroidectomy

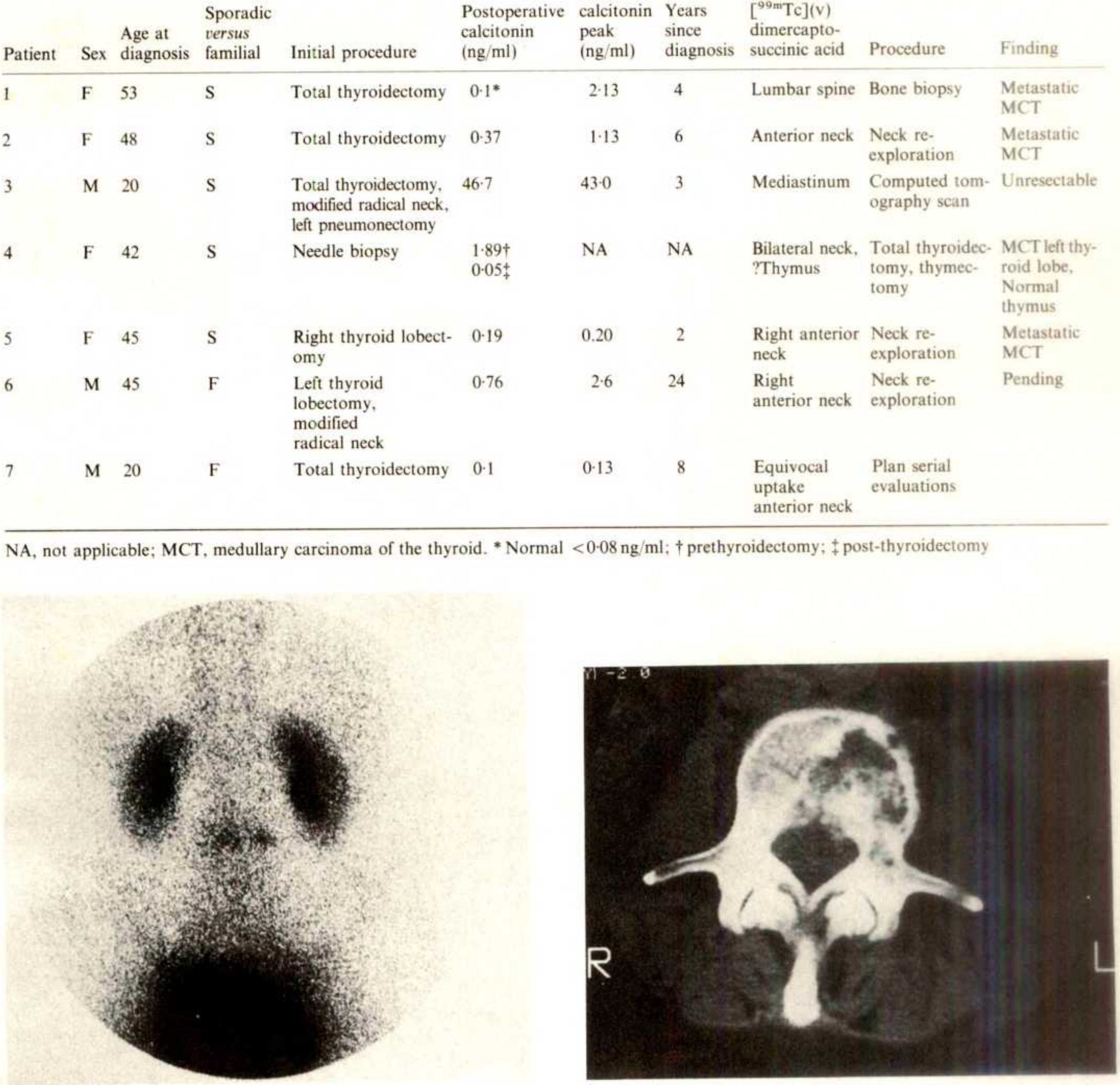

Figure 1 **a** [^{99m}*Tc*](*v*)*dimercaptosuccinic acid scintigram in case 1 demonstrating increased uptake in the lumbar vertebra. Significant uptake is also noted in the kidneys and urinary bladder.* **b** *Computed tomography scan of the third lumbar vertebra in case 1 demonstrating a lytic lesion in the vertebral body*

scan she underwent repeat cervical exploration. A palpable nodule containing metastatic MCT was found at operation in an anterior mediastinal lymph node, having been accurately localized before operation. Following removal of this the calcitonin level fell to <0·1 ng/ml.

Case 3. A 20-year-old man was noted to have a mediastinal mass on routine chest radiograph. Biopsies of enlarged right cervical and supraclavicular lymph nodes were initially interpreted as a malignant teratoma. He was referred to the John Radcliffe Hospital after he failed to respond to three courses of chemotherapy. Review of the original specimen revealed metastatic medullary carcinoma. He underwent total thyroidectomy with right modified radical neck dissection. The specimen revealed the primary focus of MCT confined to the right thyroid lobe with metastatic MCT in multiple right cervical and anterior mediastinal lymph nodes. Because of the presence of mediastinal and isolated left pulmonary metastasis he subsequently underwent left pneumonectomy and clearance of mediastinal lymph nodes. He did well postoperatively but had persistent and very high calcitonin levels (>40 ng/ml). A pentavalent DMSA scintigram demonstrated increased uptake in the mediastinum (*Figure 3*). This recurrent tumour mass has been deemed unresectable.

Case 4. This 42-year-old woman developed profuse diarrhoea with an associated 9 kg weight loss and was noted to have a left thyroid mass. A fine needle aspirate of the mass revealed MCT. Her preoperative calcitonin level was 1·89 ng/ml. A preoperative pentavalent DMSA scintigram suggested uptake in both thyroid lobes with possible uptake in the anterior mediastinum. A CT scan of the neck confirmed thyroid nodules but did not demonstrate an abnormal mediastinal mass. She underwent total thyroidectomy and cervical thymectomy. Histological review revealed two separate foci of MCT in the left thyroid lobe, diffuse nodular hyperplasia and an atrophic thymus without evidence of MCT. Her postoperative pentavalent DMSA scintigram revealed no uptake in the neck or mediastinum. Her diarrhoea resolved and the calcitonin level fell to 0·05 ng/ml.

Case 5. This 45-year-old woman underwent right thyroid lobectomy for a gradually enlarging right thyroid mass. The contralateral lobe appeared normal and there was no evidence of lymph node metastasis. A 10 × 10 cm encapsulated nodule was noted on permanent section to be diagnostic of MCT. Her postoperative course was uneventful. Her postoperative calcitonin level was elevated to 0·19 ng/ml. Pentavalent DMSA scintigraphy demonstrated a single focus of increased activity in the right anterior neck. She underwent repeat neck exploration with resection of a small residual amount of her right thyroid lobe resulting in a total thyroidectomy plus clearance of adjacent palpable enlarged lymph nodes alongside the thyroid and in the anterior mediastinum. The resected specimen revealed metastatic MCT in these nodes, which again corresponded to the site of increased activity on the scintigram. The calcitonin level in this patient has remained elevated at 0·20 ng/ml but a repeat pentavalent DMSA scintigram shows no hot spot such as was previously seen.

Case 6. This 25-year-old man was first noted to have recurrent episodes of chest pain and headaches. He did well until 1964 when he underwent a right cervical sympathectomy for Reynaud's phenomenon. During the course of the procedure he developed a rapid tachycardia and a subsequent evaluation confirmed the presence of a phaeochromocytoma. Accordingly, he underwent an abdominal exploration and a right phaeochromocytoma was removed. The left adrenal gland appeared normal. He was followed closely and in 1964 a mass was noted in the left thyroid lobe. Cervical exploration confirmed a mass in the upper left thyroid lobe and a left thyroid lobectomy was performed. In addition a parathyroid adenoma was removed. Pathological review confirmed both a well encapsulated medullary carcinoma in the thyroid and a parathyroid adenoma. The MEN 2a syndrome had by then been described as a distinct clinical entity and was clearly identified in this patient. He remained well until 1968 when metastatic disease was recognized in the left posterior triangle of the neck and he underwent a modified block dissection and subsequent postoperative radiotherapy.

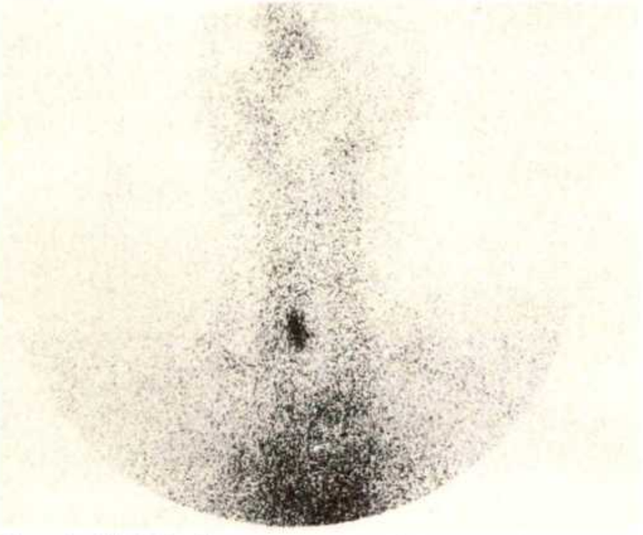

Figure 2 *[^{99m}Tc](V)dimercaptosuccinic acid scintigram demonstrating increased uptake in the lower right neck in case 2*

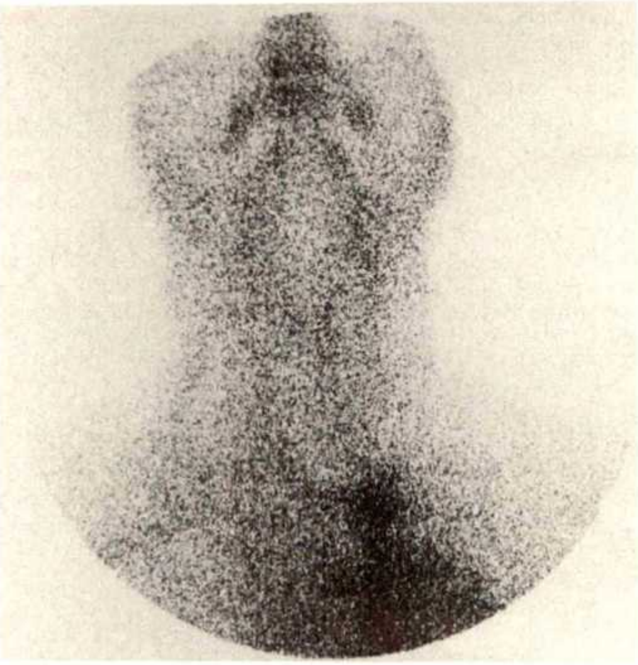

Figure 3 *Computer-enhanced [^{99m}Tc](V)dimercaptosuccinic acid scintigram demonstrating increased uptake in the right anterior neck in case 3*

In 1978 symptoms prompted a transurethral prostatectomy and he was noted to have marked hypertension during anaesthesia. A phaeochromocytoma could not be confirmed, however, until 1980 at which time he underwent left adrenalectomy.

His family history is positive for MEN 2a syndrome in a sister, nephew and two sons. His father died of 'renal disease' at age 79.

He remained asymptomatic but his calcitonin levels were persistently elevated.

A pentavalent DMSA scintigram demonstrated increased activity near the midline in the lower half of the right neck and a fine needle aspirate of the area corresponding to the right thyroid lobe has confirmed MCT. This patient awaits surgical exploration.

Case 7. This 20-year-old son of the patient in case 6 was noted to have the MEN 2a syndrome. He underwent total thyroidectomy and was noted to have MCT in both thyroid lobes. On postoperative screening, his calcitonin level was mildly elevated to 0·13 ng/ml. A pentavalent DMSA scintigram suggested increased uptake in the anterior neck. Since he has minimal calcitonin elevations, is asymptomatic and has an equivocal scintigram, repeat neck exploration was deferred pending the results of additional calcitonin tests and serial scintigraphy.

Discussion

There is broad agreement that in patients with hereditary and sporadic MCT an adequate initial cervical operation removing all thyroid tissue and lymph nodes in the primary lymphatic drainage area of the gland is required[6]. Suspicious nodes beyond the primary lymphatic drainage areas should also be dissected out.

Over the years that this strategy has evolved some patients who have and some who have not undergone such extensive surgery remain normocalcitonaemic. The expectation is that they will continue to have a good prognosis. Where initial surgery has been adequate yet local recurrence is clearly evident, then in many cases, if justified by the patient's general state of health, further surgery to reduce the tumour burden should be attempted. Although cure is then unlikely and calcitonin levels rarely return to normal, the patient can be expected to obtain worthwhile palliation. A more difficult management problem arises when a patient being followed up after adequate primary surgery for MCT shows a serial rise in plasma calcitonin, yet in whom no local recurrence or distant metastases can be demonstrated on thorough clinical examination or conventional screening. This was the situation pertaining to all cases excepting case 4 in this series. One option would have been to try to localize the source of the calcitonin production by selective venous sampling after pentagastrin stimulation – a procedure adopted with success in seven patients by Norton *et al.*[18]. However, this technique is invasive, time consuming, labour intensive and therefore expensive. Recurrent disease will be detected only if the vein draining the location is sampled, and this is unlikely to happen when a metastatis occurs in an unexpected site, as for example, in case 1 reported here. A scanning technique that facilitates identification of substantial MCT after surgery (or ideally residual disease intraoperatively) would enable the surgical strategy outlined earlier to be more effectively implemented. It was this prospect that prompted the evaluation of pentavalent DMSA scintigraphy, the experience of which to date has been limited and variable. Ohta *et al.* described four MCT patients with hypercalcitonaemia and significant tracer uptake in palpable cervical tumour and metastatic sites[14]. Although encouraging, all of these patients had bulk disease that was evident on clinical examination or conventional radiological studies. Subsequently, Hilditch *et al.* reported no uptake in any of five patients with hypercalcitonaemia[11]. This report is of particular interest because these patients were thought to have early disease with only modest calcitonin levels – the subset of patients in whom a sensitive early scintigraphic technique would have the greatest impact. The failure of these patients to concentrate pentavalent DMSA may have been due to either lack of assay sensitivity or, as suggested by Endo *et al.*[19] and Clarke *et al.*[20], technical problems with isotope preparation. More recent reports by Ramamoorthy *et al.*[15] and Clarke *et al.*[16] have been more favourable. However, all of the patients reported by Ramamoorthy *et al.* appeared to have had known metastasis, and seven of the ten patients reported by Clarke *et al.* were symptomatic at the time of study, suggesting advanced disease. In a subsequent publication, Clarke *et al.* compared the use of [^{99m}Tc](v)DMSA, [^{131}I] MIBG and [^{99m}Tc]MDP in these previously reported patients and concluded that DMSA was clearly superior[13].

Our experience with pentavalent DMSA has been particularly encouraging. In this series it has detected recurrence of MCT with sufficient accuracy to enable: further surgery to be directed to a specific site with confirmation of macroscopic disease in soft tissue (cases 2 and 5); a bone biopsy to be undertaken for an occult symptomless skeletal metastasis with histological confirmation (case 1); and a fine needle aspiration sample to be taken from an area previously deemed to be blameless with the demonstration of C cells (case 6).

No case is made in this paper for surgical intervention just on the basis of hypercalcitonaemia. Where the calcitonin is modestly elevated and stable, it is probable that the patient has microscopic residual disease which will not advance rapidly. That was the conclusion of Cance[21] and of Block *et al.*[22], the latter group operating on eight of 18 such patients and finding micrometastases in all. A normal calcitonin level was achieved in only two patients and of the remainder 12 showed stable calcitonin levels over an average of nearly 4 years. Despite the fact that significant rises in calcitonin occurred in two patients (11 per cent), extensive reoperative surgery (duration 8–12 h) as described by Tisell *et al.*[23] without any attempt to localize disease first seems hard to justify. Targeted surgery or radiotherapy, shown to be possible by pentavalent DMSA scintigraphy, is likely to have a much lower morbidity and may have a significant benefit for patients who are observed to have a rising level of plasma calcitonin.

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Protective effects of recombinant human tumour necrosis factor α and interferon γ against surgically simulated wound infection in mice

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Tumour necrosis factor α and interferon γ have both been shown to have immunoregulatory properties, and to be able to influence several microbial infections. This study showed that tumour necrosis factor was effective in modifying surgically simulated wound infections when administered both as prophylaxis and as therapy. Two models were used; one was an intramuscular bacterial challenge, and the other involved the use of a bacteria-laden thigh suture. The test bacterium for both models was Klebsiella pneumoniae, *a common surgical pathogen in our surgical service. Interferon γ was an effective biological response modifier in these models. Tumour necrosis factor was more potent than interferon γ and there was no additive or synergistic effect with interferon γ. This indicates potentially different mechanisms of action for these two cytokines.*

Keywords: Tumour necrosis factor α, interferon γ, *Klebsiella pneumoniae*, wound infection

Infection, usually occurring within the surgical wound, remains the most common postoperative complication[1]. In recent years, the principal methods of reducing wound infection rates have been to keep operative bacterial contamination of the wound to a minimum, and to prevent those organisms which do lodge in the wound from proliferating by the judicious use of prophylactic antibiotics and antiseptics[2–4]. However, antibiotics, sterile techniques and mechanical barriers have all been shown to be incompletely effective. Thus, non-specific enhancement of host defence mechanisms has the potential further to improve infection control. One possible biological response modifier that could be used for such a purpose is tumour necrosis factor α (TNF).

TNF has been shown to have several immunoregulatory activities[5,6]. These include regulation of histocompatibility antigen expression in fibroblasts[7] and of interleukin 1 production and activity[8]. Therefore, TNF could play a major role in regulation of immune response. Human TNF has been shown to be active in murine systems[5–8]. Interferon γ (IFN-γ) is another immunoregulatory cytokine which has also been shown to regulate several immune responses[9]. In addition, IFN-γ has recently been shown to modulate resistance to bacterial infections in several models of infection[10–12], perhaps as a result of its immunomodulatory properties.

The present study was carried out to determine whether TNF also could affect resistance to infection in surgical wound infection models. Two well characterized models were used. One was an intramuscular bacterial challenge. The second involved use of a bacterium-laden thigh suture which combined the clinically relevant elements of pathogenic bacteria, tissue damage and a surgical foreign body[12,13]. The test bacterium was *Klebsiella pneumoniae*, a common surgical pathogen in our surgical service.

The experiments were designed to determine whether pretreatment with TNF could have a prophylactic effect on the course of infection. Additional experiments were carried out to determine whether TNF therapy could affect an established infection. Human TNF and murine IFN-γ have been shown to act synergistically in the killing of tumour cells[7,8]. For this reason, additional experiments were carried out to determine whether a combination of TNF and IFN-γ therapy is more effective than TNF treatment alone.

Materials and methods

Experimental animals

Adult male CBA/J mice (H-2^k) weighing 20–25 g each, supplied by Jackson Laboratories (Bar Harbor, Maine, USA) were used. The animals were maintained according to AAALAC (American Association for the Accreditition of Laboratory Animal Care) standards. They were deprived of food but allowed free access to water for 24 h before bacterial challenge and were fed 4 h following that challenge[14]. Studies were performed according to National Institutes of Health guidelines under the supervision of a veterinary surgeon.

Wound infection model

The bacterium used throughout these experiments was an encapsulated strain of *K. pneumoniae* (Capsular Type II) obtained as a gift from the Institut Pasteur (Reference Strain no. 7832)[15].

Two murine models of wound infection were used.

Intramuscular challenge. K. pneumoniae was administered by 0·1 ml intramuscular injection into the right hind limb (approximately 10^3 bacteria: range 9×10^2 to $2·5 \times 10^3$ bacteria)

Thigh suture model Lengths of 3–0 blue twisted cotton suture were incubated overnight in trypticase soy broth (BBL Microbiological Systems, Cockeysville, Maryland, USA) inoculated with *K. pneumoniae* Lengths of suture attached to a French eye needle were inserted aseptically into the right thigh of the mice and the suture was cut flush with the skin at both ends.

Tumour necrosis factor

Human TNF, produced by recombinant DNA technology, was a gift from Genentech Inc. (S. San Francisco, California, USA). The TNF had specific activity of approximately 5×10^7 units/mg protein and was certified as endotoxin free, confirmed by limulus amoebocyte lysate testing (Associates of Cape Cod Inc., Woods Hole, Massachusetts, USA). The endotoxin concentration was determined to be <0·03 endotoxin units/ml with no inhibition. TNF was diluted with RPMI-1640 medium (Rosewell Park Memorial Institute, Gibco Laboratories, Grand Island, New York, USA).

In one experiment, a dose response was determined using TNF administered in daily doses in 0·1 ml subcutaneous injections into the left hind limb In all other experiments TNF was administered in daily doses of 7500 units in 0·1 ml subcutaneous injections into the left hind limb In all experiments, control animals received 0·1 ml of RPMI-1640 medium subcutaneously at the same time as TNF was administered.

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Interferon

Recombinant murine interferon γ was used in the *in vivo* experiments and was a gift from Genentech, Inc The IFN-γ had specific activity of approximately $2 \cdot 3 \times 10^7$ units/mg protein and was diluted with RPMI-1640 medium. The interferon was titred in our laboratory by means of a microplaque reduction assay using the Indiana strain of vesicular stomatitis virus on L-929 cells[16]. In this assay, one interferon unit was equivalent to 0 88 NIH G-002-904-511 reference standard units. IFN-γ was certified as endotoxin free, and independent limulus amoebocyte lysate testing confirmed that the endotoxin concentration was $<0 \cdot 06$ endotoxin units/ml with no inhibition. IFN-γ was administered in daily subcutaneous injections (7500 units in 0·1 ml) into the right hind limb. We have previously shown that IFN-γ is equally effective if administered in the same or opposite leg as the bacterial challenge[11].

Experimental design

Two experiments assessed the effect of TNF when administered for 5 days before intramuscular challenge. In the first experiment, survival of a TNF pretreated group ($n=10$) was compared with survival of a control group ($n=10$). The second experiment assessed the effect of TNF pretreatment in combination with IFN-γ. Four groups of 16 mice were studied, each pretreated for 5 days as follows: TNF, IFN-γ, TNF+IFN-γ, and RPMI-1640 medium (control)

Two experiments assessed the protective effect of TNF as therapy without pretreatment. In one, TNF treatment commenced 1 h after intramuscular challenge and was administered for 7 days. Survival of the TNF treated group ($n=32$) was compared with survival of a control group ($n=32$). The other experiment assessed the effect of TNF therapy in combination with IFN-γ therapy. We have demonstrated previously a modest but significant effect of IFN-γ therapy in this model[11]. Four groups of 20 mice, each treated as follows, were studied: TNF, IFN-γ, TNF+IFN-γ, and a control group

The next two experiments used the thigh suture model. In the first experiment, TNF or RPMI-1640 was administered daily for 5 days before suture challenge. Survival of a TNF group ($n=16$) was compared with survival of a control group ($n=16$). In the second experiment, TNF was administered as therapy without pretreatment. Treatment commenced 1 h after suture challenge and was administered for 7 days. Survival of a TNF group ($n=20$) was compared with survival of a control group ($n=20$). All surviving mice were observed for a minimum of 3 weeks after suture challenge to assess late mortality. These have been shown previously to be the most effective protocols for immunomodulation using this model[12]

In an experiment designed to assess the effect of TNF on local and systemic bacterial recovery following suture challenge, a TNF group ($n=30$) was compared with a control group ($n=40$). All mice were pretreated for 5 days before suture challenge. Eight animals from each group were killed by cervical dislocation at three time periods. 1, 2 and 3 days after suture challenge. Immediately after each animal was killed, blood was withdrawn by cardiac puncture into heparinized syringes. The medial compartment musculature, including the inserted suture, was excised *en bloc*, the suture dissected out, and its length measured with a micrometer. Blood and muscle then underwent quantitative bacteriology. The number of mice that died during the experiment was recorded.

Quantitative bacteriology

To estimate the initial bacterial inoculum, the number of bacteria per millimetre of suture was determined by homogenizing a 1 cm length of the suture with 10 ml of sterile phosphate buffered saline (PBS), using a glass mortar and an electrically driven Teflon® (Du Pont) pestle After agitation for 5 min, the homogenate was serially diluted in PBS, plated on nutrient agar (BBL Microbiology Systems, Cockeysville, Maryland, USA), incubated overnight at 37°C, and the bacterial colonies counted. The number of bacteria introduced initially into an animal was calculated from suture length Quantitative determination of the number of bacteria in the wound was performed in a similar manner. Each excised specimen of muscle, together with the inoculating suture, was homogenized and plated as above. These values are presented as a percentage of local bacterial recovery from muscle, expressed on a $\log_{10}$ scale. Blood removed by cardiac puncture (0·1 ml) was diluted serially with PBS and plated on nutrient agar. After overnight incubation, the number of colony-forming units was counted, allowing accurate assay of bacteraemia. Blood bacterial counts were expressed on a $\log_{10}$ scale.

Endogenous cytokine production

Spleen cells were removed from mice 48 h after commencement of infection in both the intramuscular and surgical wound infection models. The spleen cells were teased into individual cell cultures and placed in RPMI-1640 medium, and 5 μg/ml of phytohaemagglutinin-P was added to each culture, after which they were allowed to incubate at 37°C for 24 h. The culture supernatant fluids were harvested and assayed for cytokine activity. TNF activity was determined on L-929 cells by the method of Ruff and Gifford[17]. IFN-γ activity was determined by the microplaque reduction method of Campbell *et al*[18] using L-929 cells and the Indiana strain of vesicular stomatitis virus. In this assay, one IFN unit was equivalent to 0 88 NIH G-002-904-511 reference standard units.

Statistical analysis

Data are expressed as mean and standard error of the mean Student's *t* test for independent means was used for muscle and blood culture results. The χ^2 test with Yates' correction for continuity was used for survival data. Fisher's exact test was used if the expected value in any cell was <5. In all cases, differences were considered significant at $P<0 \cdot 05$.

Results

Effect of 5 days pretreatment with TNF on the course of intramuscular K. pneumoniae *infections in mice*

When mice were pretreated with 7500 units of TNF daily, they survived significantly longer than controls. Higher (750 000 units) or lower (750 units) doses of TNF were not as effective in prolonging survival (*Figure 1*). Seven in the TNF group survived compared with one in the control group ($P<0 \cdot 05$).

In the experiment assessing the effect of the combination of

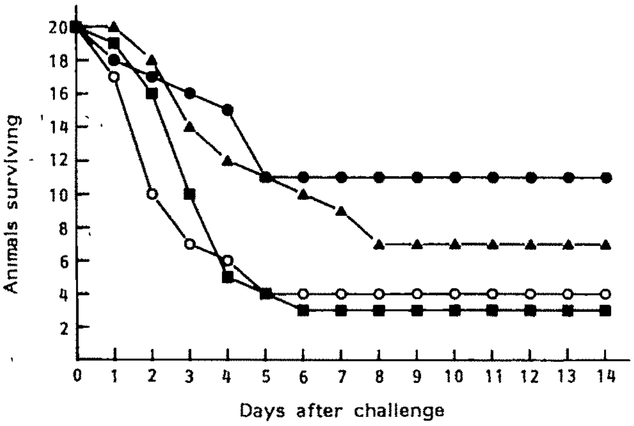

Figure 1 *Dose–response study of survival of mice treated with tumour necrosis factor (TNF) for 5 days before intramuscular* K. pneumoniae *challenge.* ○, *controls;* ■, *750 units TNF/day;* ●, *7500 units TNF/day,* ▲, *750 000 units TNF/day*

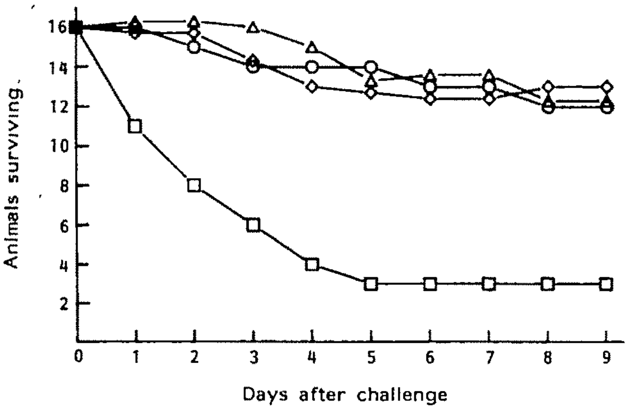

Figure 2 *Survival of mice treated with tumour necrosis factor (TNF) and/or interferon γ (IFN-γ) for 5 days before intramuscular* K. pneunoniae *challenge ncompared with controls* □, *controls;* △, *TNF,* ○, *IFN-γ,* ◇, *TNF+IFN-γ. TNF, IFN-γ and TNF+IFN-γ groups had significantly improved survival compared with controls at each day after bacterial challenge*

TNF and IFN-γ administered as a pretreatment, the TNF, IFN-γ, and TNF + IFN-γ groups all had significantly improved survival over the control group for each day after bacterial challenge (*Figure 2*). Their effects were similar. Analogous enhanced survival was observed when murine TNF was used (data not shown).

Effect of TNF therapy on course of intramuscular K. pneumoniae *infections in mice*

When treatment was started 1 h after infection, survival was markedly greater in the TNF group than in the control group from day 3 onwards. After day 6, 18 of 32 mice in the TNF group and 6 of 32 mice in the control group survived ($P < 0.05$)

In the experiment assessing the effect of the combination of TNF and IFN-γ administered as therapy, survival in both the TNF and TNF + IFN-γ groups was significantly greater than in the control group (*Figure 3*). More mice in the IFN-γ group survived than in the control group, but this difference was not statistically significant.

Effect of TNF on survival after suture challenge

The intramuscular dose of *K. pneumoniae* introduced with the sutures ranged between $2{\cdot}1 \times 10^6$ and $4{\cdot}6 \times 10^6$ organisms. In the experiment with 5 days of TNF pretreatment, the pretreated group had a survival rate that was appreciably greater than the control group from day 4 onwards. There were no further deaths after day 7. Eleven mice in the TNF group survived compared with only 3 in the control group.

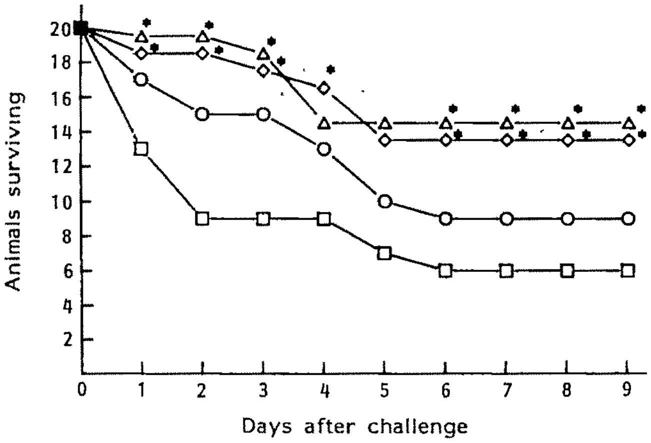

Figure 3 *Survival of mice treated with tumour necrosis factor (TNF), and/or interferon γ (IFN-γ) compared with controls, when treatment commenced 1 h after* K. pneumoniae *intramuscular challenge and continued daily for 7 days.* □, *control;* △, *TNF,* ○, *IFN-γ,* ◇, *TNF+IFN-γ,* *, *statistically significant difference from control*

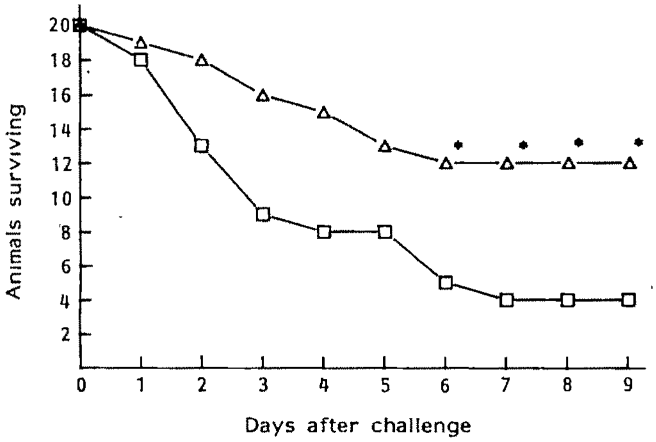

Figure 4 *Survival of mice treated with RPMI-1640 medium (controls) or tumour necrosis factor (TNF) daily for 7 days commencing 1 h after suture challenge.* □, *control;* △, *TNF;* *, *statistically significant difference from control*

Table 1 *Number of animals killed for quantitative cultures and mortality at each time period*

Time period	Mortality	Control group (n=40)	Tumour necrosis factor treated group (n=30)
Day 1	Killed	8	8
	Died	7	3
Day 2	Killed	8	8
	Died	5	2
Day 3	Killed	6	8
	Died	6	1

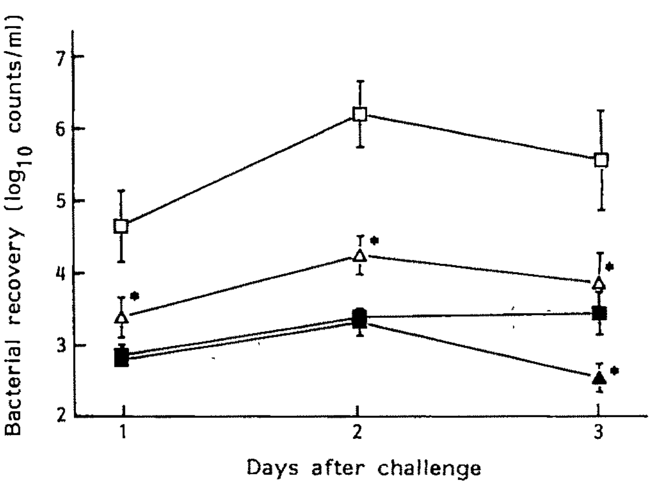

Figure 5 *Effect of tumour necrosis factor (TNF) pretreatment on systemic and local bacterial recovery from mice following suture challenge systemic recovery. Systemic recovery;* □, *control;* △, *TNF Local recovery* ■, *control;* ▲, *TNF. Error bars refer to standard error of the mean*

In the TNF therapy experiment with no pretreatment, the TNF group survived to a significantly greater extent than did the control group from day 6 onwards (*Figure 4*). There were no further deaths after day 7, and 12 mice in the TNF group survived compared with only four in the control group ($P < 0.05$).

Effect of TNF on quantitative bacterial counts after suture challenge

The number of animals killed for quantitative bacteriology is shown in *Table 1* The TNF pretreated group consistently had significantly lower systemic blood-borne bacterial counts than the control group (*Figure 5*). There was no difference in local bacterial recovery at the site of infection between the TNF pretreated group and the control group at days 1 and 2 after suture challenge. However, the TNF-pretreated group had markedly less local bacterial recovery than the control group 3 days after challenge

Production of IFN-γ and TNF by mice during models of wound infection

Control mouse spleens challenged with phytohaemagglutinin showed mean production of 7 units of IFN-γ and 6 units of TNF. Spleen cells from mice maintained in the intramuscular infection model showed no detectable IFN-γ production and 2 units of TNF. Spleen cells from mice maintained in the thigh suture infection model showed no detectable IFN-γ production and 4 units of TNF.

Discussion

TNF has been shown to have several immunoregulatory properties[5,6], which make it a good candidate for use in determining the ability of cytokines to modulate microbial infections. In this study, two well established models of surgical wound infection were used[11,12,14]. The thigh suture model combines the clinically important elements of pathogenic bacteria, foreign body and tissue damage[12,13,14].

The results of this study indicate that pretreatment of mice with TNF for 5 days before intramuscular infection with *K. pneumoniae* resulted in enhanced survival of those mice compared with controls. Similar effects were seen in the thigh suture model in which mice pretreated with the same regimen of TNF had significantly improved survival compared with controls. This is in agreement with previously reported work from Parant and coworkers[15,16], which indicated that both crude and pure preparations of TNF resulted in protection in mice from *K. pneumoniae*, as well as from several other bacterial and fungal infections[19].

It would also appear that TNF is protective even when given after initiation of bacterial infection. When TNF was administered therapeutically after bacterial inoculation, survival of mice was enhanced appreciably compared with controls, in both the intramuscular challenge and the thigh suture models. However, neither model showed an enhancement of survival with TNF therapy as great as that demonstrated when TNF was administered as a pretreatment. Nevertheless, the fact that TNF therapy was effective might ultimately prove to be of importance if TNF can be shown to be safe and to give consistently reproducible results. Previous studies with IFN-γ have indicated a limited protective effect in the 1 h therapy in *K. pneumoniae* model, and TNF may be more effective than IFN-γ[11]. Selection of an appropriate dose of TNF is crucial. In this study a low dose of TNF was selected because of the known detrimental effects of high doses[20]. Indeed, TNF may be one of the endogenous mediators of septic shock[20]. In murine models of septic shock, in which high circulating levels of endogenous TNF are present, the administration of polyclonal antisera directed against TNF actually improved survival[21]. Thus, it would appear that TNF has a narrow therapeutic index. In the animal models used in this study, a 100-fold increase in TNF dosage resulted in toxic effects.

Using the thigh suture model, it was possible to determine the effect of cytokine treatment on systemic and local bacterial recovery in addition to its effect on survival[12,13,14]. Earlier studies have indicated that IFN-γ pretreatment of mice before thigh suture resulted in decreased mortality[12]. In addition, counts of blood-borne bacteria, but not bacteria isolated from the wound site, were decreased in IFN-γ treated mice[11]. This study showed that bacterial recovery from the blood of TNF-pretreated mice was decreased significantly compared with controls. Bacterial recovery from local wound sites was reduced significantly on the third day after suture challenge in TNF-pretreated mice. This suggests that TNF has both local and systemic effects on bacterial recovery, in contrast with previous reports on IFN-γ, and suggests that it has a different mechanism of action from IFN-γ.

Previous reports have suggested a synergistic effect of TNF and IFN-γ when both were used in tumour models[5,6]. Potentially synergistic or additive effects of TNF and IFN-γ were examined in the intramuscular challenge model. When mice were pretreated with cytokines for 5 days before infection, survival was enhanced markedly in mice pretreated with INF-γ compared with controls. Mice pretreated with TNF or the combination of TNF and IFN-γ also had a significantly improved survival compared with controls. There was no difference in survival of mice between the three cytokine treatment groups at any time. Although synergy between TNF and IFN-γ was not demonstrated, survival was so dramatically improved in all three cytokine treatment groups that it may have been impossible to demonstrate synergy in this experiment.

When the cytokines were administered solely as therapy, commencing 1 h after bacterial challenge, there was a trend toward enhanced survival in the IFN-γ therapy group, as previously reported[11]. In the present study this trend did not reach the statistically significant levels seen in the previous study[11], perhaps as a result of the sample size used. Both the TNF group and the TNF+IFN-γ combination group had appreciably enhanced survival. There was no difference in survival between the TNF group and the TNF+IFN-γ combination group. Again no synergistic effect between TNF and IFN-γ was shown.

The results of this study demonstrate that TNF is a very effective immunomodulator in models of surgical wound sepsis at doses far below those inducing toxic effects[22–25]. The dose of 7500 units of TNF (6 μg/kg) is below both the dose noted by Schirmer *et al.* (1 mg/kg) not to affect cardiac output, heart rate or renal blood flow in rats[21], and the dose (0·6 mg/kg) used by Tracey *et al.* that resulted in tachypnoea, hypotension and 36 per cent mortality rate in rats[22]. The fact that TNF was effective when administered as therapy, commencing after bacterial challenge, is especially encouraging. In addition, endogenous TNF and IFN-γ production appears to have been compromised during these experiments in surgical wound infection. TNF, therefore, may have the potential to enhance the immune response in infected patients and may be helpful when bacterial infection is refractory to antibiotic therapy.

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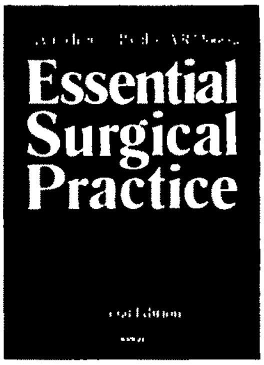

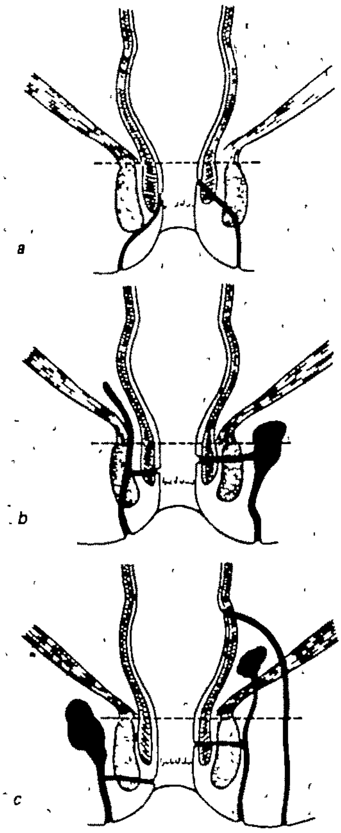

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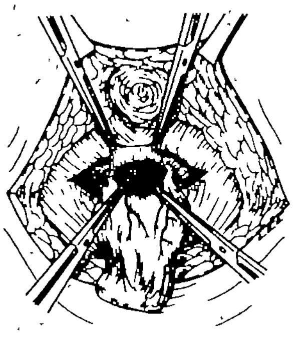

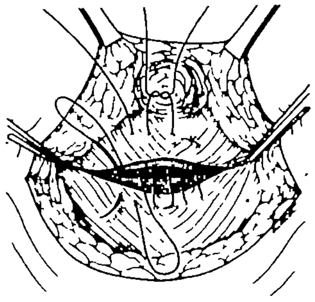

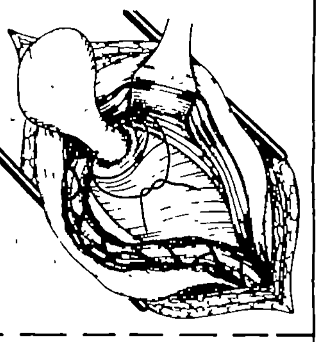

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Diurnal insulin and glucose profiles following transplantation of fresh and cryopreserved canine pancreatic islets

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Dispersed islet autotransplants (fresh and cryopreserved) can produce normal fasting insulin and glucose concentrations. Following an intravenous glucose challenge, however, the insulin response is impaired and glucose clearance delayed. This study examines the diurnal insulin and glucose response to feeding in recipients of fresh islet autografts ($n=6$), *recipients of cryopreserved islet autografts* ($n=3$), *normal unoperated controls* ($n=10$) *and insulin treated pancreatectomized diabetic dogs* ($n=7$). *Mean fasting insulin and glucose levels were similar in all groups. After feeding, insulin profiles in both transplant groups were near normal while significant hyperinsulinaemia occurred in insulin treated diabetic dogs. Mild postprandial carbohydrate intolerance was observed in transplant recipients but glycosylated haemoglobin levels were similar (mean(s.d.)) to normals (6·88(0·86) per cent, 6·86(0·5) per cent respectively). Dispersed islet autotransplantation with portal insulin delivery produces near normal insulin and glucose profiles suggesting that this may represent a suitable treatment for insulin dependent diabetes.*

Keywords: Pancreatic islet transplantation, cryopreservation, insulin profiles, glucose profiles

The discovery of the link between the pancreas and diabetes by Minkowsky and von Mering in 1889[1] led to an interest in pancreatic transplantation as a treatment for the disease. In 1893 Williams in Bristol transplanted fragments of a sheep's pancreas into a diabetic boy. Although he could not convincingly demonstrate function, he expressed optimism in the principle[2]. With the discovery and availability of injectable insulin it was hoped that metabolic abnormalities would be corrected and a normal life ensue. While death from ketoacidosis was avoided it soon became apparent that secondary changes occurred in the tissues of diabetics which led to increased morbidity and mortality compared with the normal population[3].

The aetiology of diabetic complications remains unclear but is likely to be related to persistent metabolic abnormalities[4]. All forms of current therapy administer insulin peripherally and are associated with elevated insulin levels. Certain diabetic complications have been attributed to hyperinsulinaemia[5] and deterioration of intermediary metabolism has been associated with intensified insulin therapy[6].

Dispersed intrasplenic islet transplantation is intended to correct intermediary metabolism by supplying insulin and counter-regulatory hormones in a physiological manner. These grafts possess a number of practical advantages over pancreatic segments. For instance, they can be stored indefinitely by cryopreservation and can be safely injected into a portally draining site for optimum insulin delivery. Both fresh[7] and cryopreserved[8] grafts have been shown to correct levels of insulin, glucose and intermediary metabolites in the fasting animal. Following an intravenous glucose challenge, however, the insulin response is impaired and glucose clearance delayed. The significance of this for response to normal daily challenges of food and exercise is unknown.

The purpose of this study, therefore, was to examine diurnal glucose and insulin profiles in dogs with islet autotransplants (fresh or cryopreserved) and to compare them with two other groups; normal dogs and pancreatectomized diabetic dogs treated with twice daily insulin injections.

Materials and methods

Twenty-six male and female mongrel dogs weighing between 12 and 24 kg were used in the study. The experimental groups were:

Group 1

Ten unoperated dogs acted as normal controls.

Group 2

Seven animals underwent total pancreatectomy and received twice daily insulin injections. Frequent determinations of blood glucose were made each day before the study to establish the dose of insulin that was sufficient to maintain a fasting blood glucose of less than 12 mmol/l. The study was performed 10–14 days after pancreatectomy to avoid problems with the interpretation of insulin results as a consequence of insulin antibody formation.

Group 3

Six animals received a dispersed pancreatic autotransplant as described previously[7] and were studied at 10–12 weeks after transplantation.

Group 4

Three animals received a dispersed pancreatic graft prepared as for group 3 but cryopreserved as previously described[9] and stored in liquid nitrogen at −196°C for 2 weeks. These animals were studied at 10–12 weeks after transplantation. Four other recipients of cryopreserved grafts suffered graft failure before 10 weeks and were not considered in this study.

Each study was performed following an overnight fast. On the morning of the study a heparinized 21G (0·80 × 40 mm) cannula was inserted into a foreleg vein at 05.30 hours. Blood samples for glucose and insulin determinations were taken at intervals of 2 h from 06 00 to 22.00 hours. Animals were fed a standard meal at 10.00 hours and again at 16 00 hours. Further blood samples were taken at intervals of 5, 10, 15, 20, 30, 45, 60 and 90 min after each meal. This protocol was modified in the insulin treated group where subcutaneous insulin was administered at 10.00 hours and 16 00 hours with feeds. In addition to the 2-hourly samples blood was taken 30 and 60 min after meals. All samples were stored on ice and plasma glucose was assayed on the day of the experiment. The plasma for insulin determination was

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Based on a paper presented to the British Association of Endocrine Surgery at Edinburgh in May 1987

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separated and stored at $-20°C$ for batch assay at a later date by methods described previously[7]. Glycosylated haemoglobin levels were assayed in normal dogs and in the recipients of fresh islet grafts at intervals of 1 month. The monthly results were pooled and compared with the normal range.

Test meal

The morning meal consisted of 750 g proprietary dog food (Chum, Pedigree Foods Ltd., Melton Mowbray, UK) and 150 g of food mixer (Chum Mixer, Pedigree Foods Ltd.). The afternoon meal consisted of 375 g dog food and 75 g mixer. Pancreatectomized dogs received pancreatic exocrine replacement therapy (Pancrex V® powder, Paines and Byrne, Greenford, UK). These quantities of food maintained weight in pancreatomized dogs

Statistical analysis

Comparison of values within groups at different times was performed using Wilcoxon's signed rank test for paired data. When comparing different groups Wilcoxon's rank sum test for unpaired data was used. When comparing fasting values within or between groups the 10.00 hours determinations were used and when comparing fasting with fed values the peak postprandial values were used. Groups were also compared at each time point during the study using Wilcoxon's rank sum test.

Results

Group 1 (Controls)

Glucose profiles. Control animals had glucose profiles which varied little throughout the day (*Figure 1*). Lowest mean values were observed at 10.00 hours. Both meals were followed by a significant rise in plasma glucose levels ($P<0{\cdot}05$) with the greater increase following the afternoon meal. The most striking feature was the narrow range of glucose concentrations during the 16 h study period, plasma glucose never exceeding 6 mmol/l.

Insulin profiles. Mean peripheral insulin concentrations showed a trough at 10.00 hours (17·1 milliunits per litre)

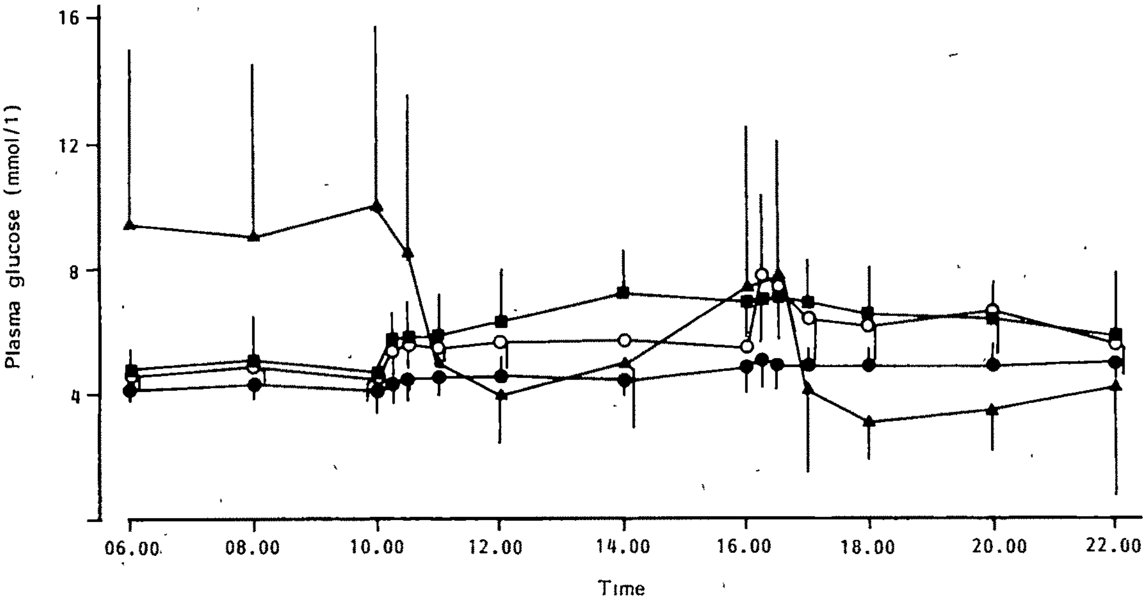

Figure 1 *Diurnal plasma glucose profiles* ●, *normal dogs* (n = *10*), ■, *recipients of fresh islet autografts* (n = *6*), ○, *recipients of cryopreserved islet autografts* (n = *3*); ▲, *insulin treated pancreatectomized diabetic dogs* (n = *7*). *Meals (and insulin injections in diabetic dogs) were supplied at 10.00 hours and 16.00 hours*

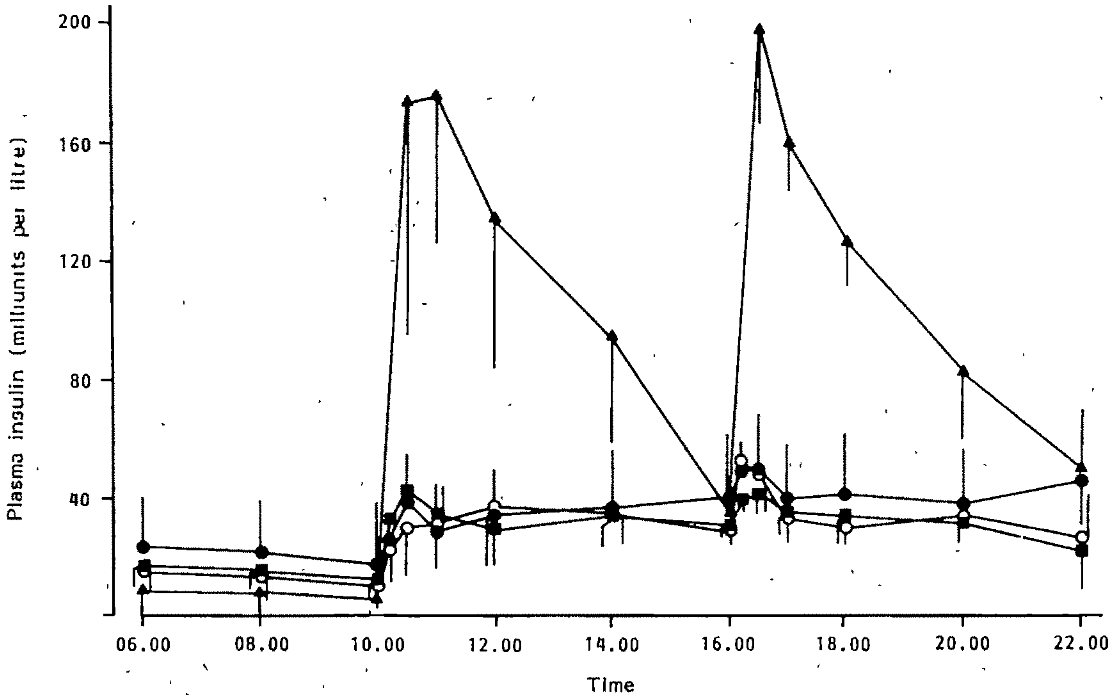

Figure 2 *Diurnal plasma insulin profiles. Key as in* Figure 1

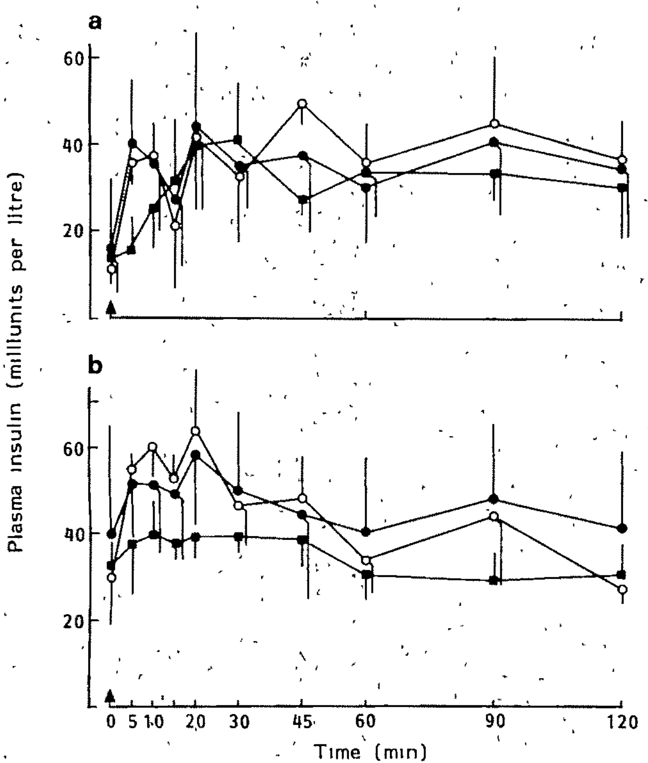

Figure 3 *Insulin response to morning meal (a) and afternoon meal (b) Key as in* Figure 1 *but with the insulin treated group omitted for clarity Arrowheads show feeding time*

(*Figure 2*). The insulin response to the morning meal was biphasic (*Figure 3*). The first peak was seen at 5 min (41·3 milliunits per litre) with a further peak of 44·6 milliunits per litre at 20 min. The response to the afternoon meal was also biphasic rising to 52·2 milliunits per litre at 5 min with a second peak of 58·4 milliunits per litre at 20 min (*Figure 3*).

Group 2 (Insulin treated diabetics)

Glucose profiles. Mean fasting glucose levels were similar to those of group 1 but the range of values was greater (*Figure 1*). Glucose concentrations fell after feeding but only the afternoon reduction was significantly different from normal, between 17.00 hours and 22 00 hours ($P<0{\cdot}05$). The animals in this group were closely observed and no hypoglycaemic signs were detected.

Insulin profiles. Mean fasting insulin concentrations were similar to those in normal animals but with a wider range of values (*Figure 2*). Following meals the mean insulin concentrations peaked at 30 min at levels of 175 milliunits per litre and 200 milliunits per litre respectively, significantly higher than controls and transplanted groups ($P<0{\cdot}01$), returning towards basal levels over the next 6 h (*Figure 2*).

Group 3 (Fresh islet graft recipients)

Glucose profiles The mean fasting plasma glucose concentrations were not significantly different from normal controls (*Figure 1*). Mild postprandial carbohydrate intolerance was observed, especially after the afternoon meal. Levels were significantly elevated compared with normals from 10.15 hours onwards ($P<0{\cdot}01$) returning to normal at 22.00 hours (*Figure 1*). In no animal did the blood glucose exceed 9·5 mmol/l at any time.

Insulin profiles. The mean fasting peripheral insulin concentrations were not significantly different from normal controls and the overall diurnal pattern was similar (*Figure 2*) but the biphasic response to meals was lost (*Figure 3*). The insulin response to the morning meal was slow to peak; the values at 5 min were significantly reduced compared with normals ($P<0{\cdot}05$). The response to the afternoon meal was blunted, though this difference only reached significance at 20 min ($P\leq0{\cdot}05$).

Glucose 4 (Cryopreserved islet graft recipients)

Glucose profiles. The cryopreserved transplant recipients had glucose profiles similar to group 3 with normal fasting glucose levels and mild postprandial carbohydrate intolerance (*Figure 1*).

Insulin profiles. The mean insulin profiles were similar to those seen in group 1 and, in particular, the biphasic response to meals was preserved (*Figures 2* and *3*).

Glycosylated haemoglobin levels

In recipients of fresh grafts glycosylated haemoglobin levels (6·88 (0·86 per cent)) were similar to those of normal controls (6·86 (0·5 per cent)) throughout the study period.

Discussion

The aims of pancreatic transplantation are to restore insulin independence and to prevent the secondary complications of diabetes. There is no convincing evidence that established diabetic complications can be reversed[10–12].

Some success has been achieved using vascularized pancreatic segment transplantation and many patients have become insulin independent. Its use remains restricted to patients in end-stage disease or to diabetic recipients of a renal transplant in whom an added burden of immunosuppression does not require justification. The morbidity and mortality rates of the technique, however, suggest that it is unsuitable for patients with early disease, the very patients in whom complications might be preventable[13].

Dispersed islet grafts, on the other hand, can be placed into a site with portal venous drainage and do not have the risks of pancreatic fistula or vascular thrombosis. It is important to establish that such grafts provide near normal diurnal insulin delivery in response to daily dietary challenges and might thereby prevent the development of secondary complications

Our study has demonstrated that the insulin response from a dispersed fresh or cryopreserved islet graft to a mixed meal was similar to that seen in normal animals. This is different from previous studies which employed intravenous glucose tolerance tests to assess graft function and demonstrated poor insulin response despite normal fasting insulin and glucose levels[7,14,15]. These studies called into question the ability of islet grafts to restore normal metabolism.

The difference between the present and previous studies may be attributed to the route of nutrient delivery. The secretion of insulin occurs at a rate determined by blood glucose and modulated by neural and endocrine influences. Oral ingestion of carbohydrate[16] and amino acids[17] is more effective than parenteral administration of the same quantity and the term 'entero-insular axis' has been coined to embrace those gut factors which contribute to the enhanced insulin response to ingested nutrients[18]. Insulin release following food is biphasic with an initial peak after 2 min followed by a more prolonged plateau response starting 5–10 min after the meal. The initial response is thought to be neurogenic owing to the release of acetylcholine and possibly other peptides from nerve endings terminating on the islet cell wall[19] When islets are denervated, as in islet grafts, the initial response is lost which is consistent with the absent first phase insulin response to the morning meal in the present study. Certain gastrointestinal hormones, however, that are potent stimulators of insulin secretion (e.g gastroinhibitory polypeptide[20]), are released in response to vagal activity and intraluminal nutrients. This probably accounts for the near normal diurnal profile in this study.

The intravenous glucose tolerance test has been used to assess islet graft function in most other studies of pancreatic islet transplantation. Nevertheless, it may not be suitable for studying the dispersed, denervated, heterotopically located islet graft as it disregards the response of the entero-insular axis and probably underestimates the true functional reserves of the graft

Neither group of transplanted animals exhibited hyperinsulinaemia when compared with the insulin treated group in which plasma insulin concentrations four times those of normal controls were required to achieve postprandial euglycaemia. This is consistent with the findings of Tchobroutsky where four- to fivefold increases in insulin concentrations were required to achieve euglycaemia in insulin treated diabetics[21]. Insulin is normally delivered into the portal vein and a significant proportion is extracted by the liver, which results in a difference (of between two and ten times) in insulin concentration between portal and peripheral blood[22]. Current insulin therapy, continuous subcutaneous insulin infusion and segmental transplantation all result in hyperinsulinaemia because of peripheral insulin delivery, and persistent hyperinsulinaemia has been implicated in the pathogenesis of certain diabetic complications[5].

Mild postprandial carbohydrate intolerance was demonstrated in animals with both fresh and cryopreserved grafts. Islet denervation resulting in the loss of the initial insulin response may have contributed to the mild intolerance following the morning meal. A suboptimal islet mass may account for the blunted insulin response to the afternoon meal in group 3 animals. While as little as 13 per cent of the intact pancreas will maintain normal fasting blood glucose levels, glucose tolerance is impaired when more than 50 per cent of the intact canine pancreas is removed[23] Our dispersed islet implant mass was difficult to quantify and was unknown in these transplants but Kretschmer *et al*., using a similar method of graft preparation, estimated the islet yield as 7·4 per cent[24]. However, their grafts were associated with low fasting insulin levels and an insignificant response to a glucose challenge which suggests that the yield in the current study was considerably greater.

It is unclear whether mild carbohydrate intolerance with near normal insulin levels would be significant in terms of diabetic complications. Glycosylated haemoglobin levels in transplanted animals remained within the normal range throughout the period of study and at 27 months after transplantation no evidence of diabetic retinopathy has been detected[25].

Cryopreserved graft recipients had a normal diurnal insulin response to meals confirming that ultralow temperature storage did not result in permanent injury to insulin production or release mechanisms[26]. In another study the insulin response to an intravenous glucose tolerance test in a group of recipients with cryopreserved grafts was greater than that of fresh graft recipients[8] and Warnock *et al.* found that the duration of hyperglycaemia following an oral carbohydrate load was shorter in recipients with cryopreserved grafts[27]. He attributed this to the 'purifying effects' of cryopreservation on the potentially harmful exocrine contaminants.

Dispersed islet grafts transplanted to a portally draining site restore near normal diurnal insulin and glucose profiles. Function is maintained following cryopreservation If the problems of islet harvesting and rejection can be overcome these grafts might prevent the secondary complications of diabetes when transplanted to newly diagnosed insulin dependent diabetics.

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Technical training in surgery: the trainee's view

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A questionnaire designed to investigate the technical training of general surgical trainees was distributed throughout Scotland. A total of 222 questionnaires were sent out and 179 (81 per cent) were returned. Of the responders, 38 per cent felt that the overall operative workload was too small and the majority thought that there was too little emphasis on supervised operating. Two-thirds of trainees were generally satisfied with the amount of unsupervised operating, although a substantial proportion (21 per cent) sometimes felt out of their depth when performing delegated emergency operations. Few had attended craft workshops or travelled to other centres, but of those who had, most considered both activities to be very useful. Photographic atlases and videos were not generally felt to be of great value by those who had used them. The majority of trainees did not believe that research activity had interfered excessively with their technical training.

Keywords: Technical training, general surgery

Despite the obvious importance of technical training in surgery, there has been little attempt to study the way in which operative skills are taught in this country. Furthermore, although there is a resurgence of interest in training[1–6] it is clear that not all surgeons are entirely happy with current methods[7,8]

Before devising ways of improving the present system of teaching practical surgery, it is important to identify possible areas of weakness In an attempt to do this, a survey of junior surgeons throughout Scotland has been carried out to assess their attitudes towards training.

Method

The questionnaire did not include personal details other than training grade, thus preserving the anonymity of both responder and centre It was mailed to 222 general surgical trainees who were identified by personal contact with 25 Divisions of Surgery in teaching and district general hospitals A specimen questionnaire was sent to each institution, and in no instance was permission to circulate it refused. We believe that almost all general surgical trainees in Scotland were contacted by this means

The questionnaire was divided into four main sections

Section I was designed to investigate operating workload by ascertaining the number of half-day sessions spent in the operating theatre per week, each trainee was also asked whether the amount of time spent in theatre assisting, being assisted by a senior member of staff or operating alone was satisfactory.

Section II asked the trainees whether delegation of cases was appropriate, and in particular whether they ever felt out of depth when operating alone.

Section III explored the perceived role of photographic atlases, videos, surgical workshops and travel to other centres to watch recognized experts operate

Section IV posed the question. 'Do you feel that the need for doing research and writing scientific papers has diverted your attention excessively from training in the technical aspects of surgical practice?'

Results

Of the 222 questionnaires sent out, 179 (81 per cent) were returned. It was impossible to evaluate eight because the trainee was in a post which did not involve operative surgery; this left 171 (77 per cent) replies available for analysis. Twenty-five came from senior registrars and 146 from registrars or senior house officers, 64 were returned from district general hospitals and 107 from teaching hospitals. Only two of the senior registrars were at district general hospitals at the time of circulation.

The number of half-day sessions spent by trainees in the operating theatre each week is shown in *Figure 1* This varied from no regular sessions to seven, but the majority of trainees worked three or four. When asked to give a subjective opinion on workload, most felt that it was satisfactory, although a sizeable proportion thought that there was too little, and only one considered that there was too much (*Table 1*). The proportion of trainees who were dissatisfied with the operative workload was smaller in the district general hospitals than in teaching hospitals.

Operating theatre experience was subdivided into three categories: assisting, supervised operating and operating alone. The trainee surgeons were asked if they were exposed to the right amount, too little or too much of each of these categories. Very few thought that they did too little assisting, but the majority felt they had too little supervised operating and a large minority considered that there was too little operating alone. On the other hand, assisting was the only one of the three areas in which a significant number of trainees thought there was too much (*Figure 2*).

Trainees' attitudes to the degree of difficulty of operations they were expected to perform unsupervised were then investigated The replies (*Tables 2* and *3*) indicated that most

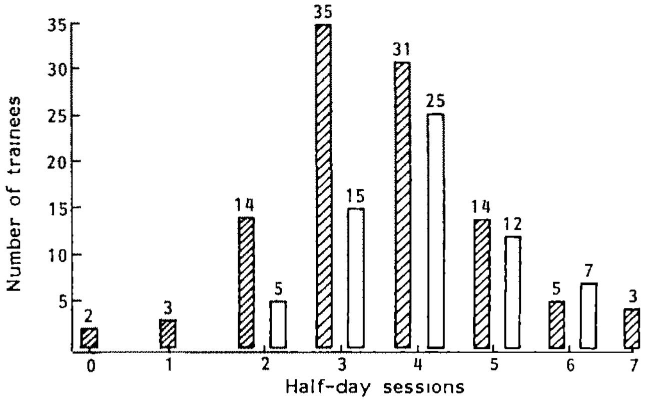

Figure 1 *Distribution of operative workload expressed as half-day sessions per week* ■, *teaching hospital;* □, *district general hospital*

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Table 1 *Operative work load*

	Total	Senior registrar (*n*=25)	Registrar/ senior house officer (*n*=146)	Teaching hospital (*n*=107)	District general hospital (*n*=64)
Too little	65 (38)	8 (32)	57 (39)	50 (47)*	15 (23)*
Right	105 (61)	16 (64)	89 (61)	56 (52)	49 (77)
Too much	1 (1)	1 (4)	0 (0)	1 (1)	0 (0)

Values given are number of replies with percentages in parentheses. * $\chi^2=9{\cdot}5$, $P<0{\cdot}01$

Table 2 *Elective operating alone*

	Total	Senior registrar (*n*=25)	Registrar/ senior house officer (*n*=146)	Teaching hospital (*n*=107)	District general hospital (*n*=64)
Too minor	39 (23)	5 (20)	34 (23)	26 (24)	13 (20)
Right level	116 (68)	17 (68)	99 (68)	70 (66)	46 (72)
Sometimes out of depth	16 (9)	3 (12)	13 (9)	11 (10)	5 (8)

Values given are number of replies with percentages in parentheses

Table 3 *Emergency operating alone*

	Total	Senior registrar (*n*=25)	Registrar/ senior house officer (*n*=146)	Teaching hospital (*n*=107)	District general hospital (*n*=64)
Too minor	13 (8)	0 (0)	13 (9)	12 (11)	1 (2)
Right level	121 (71)	20 (80)	101 (69)	79 (74)	42 (66)
Sometimes out of depth	37 (21)	5 (20)	32 (22)	16 (15)*	21 (32)*

Values given are numbers of replies with percentages in parentheses. * $\chi^2=7{\cdot}5$, $P<0{\cdot}01$

Table 4 *Effect of research on technical training*

	Total	Senior registrar (*n*=25)	Registrar/ senior house officer (*n*=146)	Teaching hospital (*n*=107)	District general hospital (*n*=64)
Excessive interference	64 (37)	8 (32)	56 (38)	40 (37)	24 (38)
No excessive interference	107 (63)	17 (68)	90 (62)	67 (63)	40 (62)

Values given are numbers of replies with percentages in parentheses

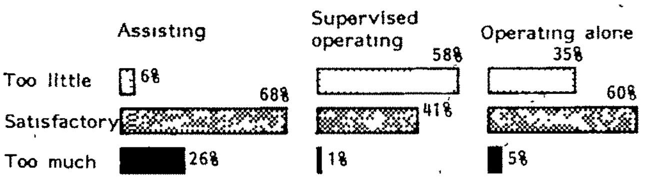

Figure 2 *Summary of trainees' attitudes to the three components of operating theatre experience*

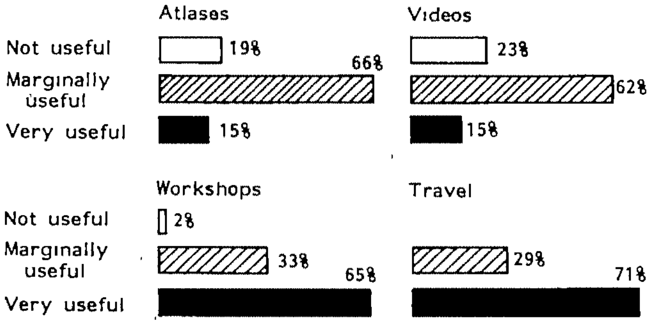

Figure 3 *Trainees' attitudes towards four adjuncts to technical surgical training: atlases (used by 107 trainees, 63 per cent), videos (used by 53, 31 per cent); workshops (used by 48, 28 per cent), and travel (used by 34, 20 per cent)*

thought such operations were at the right level of difficulty, but it is worrying to note that although only 9 per cent sometimes felt out of their depth while performing elective operations, this figure rose to 22 per cent for emergency procedures. Another important finding was that the percentage of trainees who were sometimes operating beyond their capabilities in emergency procedures was significantly greater in district general hospitals (32 per cent) than in teaching hospitals (15 per cent).

Four other aspects of surgical training were also examined (*Figure 3*). Photographic atlases had been used by many, but most had found them only marginally useful. Similarly, although videos had been used by a smaller proportion, they were not often considered to be very useful. Conversely, both workshops and educational travel were rated highly, but relatively few had experienced either.

Finally, the majority of responders did not feel that research had interfered excessively with their technical training (*Table 4*). However, in the interests of simplicity, no queries regarding the amount of research were included, and it is possible that a considerable number of the registrars and senior house officers had no research experience.

Discussion

Little is known of surgical trainees' attitudes to their own training, but in a recent small study from the Mersey region, only nine out of 16 postfellowship registrars considered their training to be good[9]. Although the median number of major operations performed or assisted at over a 3-month period was 30, the median number of supervised operations was only three. In a larger questionnaire study from America, Ritchie and Cohn questioned 922 final-year residents and found that over 80 per cent of the respondents acted as the operating surgeon in more than two-thirds of cases, supervision being provided in roughly 50 per cent of these[10]. It is impossible to make a direct comparison between these two studies, but it does seem that in the USA supervised operating is more common than in the UK, even among senior trainees From our study, it is evident that general surgical trainees in Scotland feel that too little emphasis is placed on supervised operating, and that some juniors are unhappy about being left alone, especially in emergency situations.

Good surgical technique is of vital importance and trainees should not have to acquire it at the expense of their patients. However, there is evidence that junior surgeons do sometimes operate beyond their capabilities, with detrimental effects. For example, the majority of benign bile duct strictures are caused by inexperienced surgeons performing cholecystectomies without senior assistance[11,12], and the recent Confidential Enquiry into Perioperative Deaths has highlighted inadequate consultant supervision as one of the major factors contributing to avoidable mortality[13]. The marked variability in the results of surgical operations across the country is a related phenomenon[14–17], which may be partly ascribed to lack of uniformity of technical expertise. It has been shown that technical factors probably constitute the main determinant in the development of postoperative complications[18].

Clearly, then, more emphasis should be placed on technical training, and the answers to the questionnaire described in this article suggest some areas where improvements could be made. Adequate supervision in the operating theatre should be available, not only for the safety of patients but also for the benefit of trainees. However, if more operating is to be done by surgical trainees assisted by senior surgeons, it is inevitable that the procedures will take longer. Allowance must be made for teaching in the assessment of theatre usage, waiting lists and consultant staffing levels.

In view of the favourable reaction to workshops, a more structured approach to the initial teaching of surgical skills should perhaps be adopted, with the wider use of simulated procedures. There is some evidence that such an approach can pay dividends at an early stage of training[5,19]. The workshop may also be suitable for teaching more senior trainees the rudiments of complex modern techniques. Travel to centres of surgical excellence is also considered to be useful, and appropriate opportunities could be built into training schemes. Most could probably be gained from such visits at a fairly advanced stage of training, when nuances of technique would be more easily appreciated.

In recent years, technical training has perhaps received less attention than it deserves. Now may be time to redress the balance We believe that this survey highlights some deficiencies and may be of value in the structuring of future training programmes

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Long acting somatostatin analogue in dumping syndrome

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The effect of long acting somatostatin analogue, SMS 201-995, on postprandial dumping syndrome was studied in eight patients with Billroth II gastric resection. Each patient was subjected to two oral glucose challenges with 75 g glucose. One challenge was premedicated with 50 µg SMS 201-995 subcutaneously 15 min before the oral intake of glucose, the other with placebo. With placebo all patients experienced the subjective symptoms of the early dumping syndrome with significant ($P<0.001$*) increases (mean (s.d.)) in pulse rate (from 66 (8) to 102 (10) beats/min), in packed cell volume (from 0·36 (0·05) to 0·43 (0·1) l/l) and in the plasma levels of vasoactive intestinal polypeptide (from 3·0 (0·5) to 10·2 (1·8) pmol/l). During the somatostatin study the subjective symptoms and the changes in the various parameters were not detected. In the control study seven patients showed postprandial hypoglycemia. In these patients significant elevations (*$P<0.001$*) in the insulin level (from 10 (0·9) to 40 (9·1) µE/ml) and gastric inhibitory peptide (GIP) concentration (from 100 (13) to 220 (41) ng/l) were seen, compared with the initial values. During the application of SMS 201-995 hypoglycaemia did not develop and plasma insulin and GIP concentrations remained unchanged. These results indicate that the long acting somatostatin analogue alleviates the symptoms of early and late postprandial dumping syndromes.*

Keywords: Dumping syndrome, long acting somatostatin analogue, gastrointestinal hormones

Dumping syndrome can be a serious complication after gastric surgery. Investigations have shown that the release of gastrointestinal hormones plays an important role in the appearance of symptoms[1,2,3]. Other investigations have demonstrated that native cyclic somatostatin has a beneficial effect on symptoms associated with the dumping syndrome[4,5]. The benefit of somatostatin is based theoretically on its ability to block hormone release. Recently a new long acting somatostatin analogue was developed[6]; with its long action and simple subcutaneous administration it has some advantages compared with native somatostatin. The effect of long acting somatostatin analogue on the symptoms characteristic of the dumping syndrome has been investigated

Patients and methods

Eight male patients who had developed symptoms of early and late dumping syndromes following Billroth II gastric resection were investigated during this trial (mean age, 51 years). Each patient underwent two oral glucose challenges with 75 g glucose in a standard 150 ml dose of 50 per cent glucose. One of the challenges was premedicated with 50 µg SMS 201-995 (Sandostatin®, Sandoz, Basel) subcutaneously 15 min before the oral intake of glucose; the other challenge was premedicated with placebo (isotonic sodium chloride). The premedications were assigned in double blind fashion and random order. The patients gave informed consent.

The subjective symptoms of the patients (palpitation, dizziness, fainting, vomiting and abdominal distension), as well as the pulse rate and the blood pressure were monitored at 5 min intervals during the trial. Blood was withdrawn without venous occlusion for determination of packed cell volume, glucose, insulin, gastric inhibitory polypeptide (GIP) and vasoactive intestinal polypeptide (VIP) levels determined by standard techniques and radioimmunoassays (Immuno Biological Laboratories GmbH, Hamburg, FRG).

Blood samples were taken 15 min before the glucose administration, at zero time and every 30 min during the total 240 min following the challenge The results of the two glucose challenges were compared using Student's paired *t* test.

Results

The baseline parameters of patients in the two studies did not show any statistical differences. The levels of the investigated hormones were normally distributed in this study and the standard deviations were relatively low.

In the placebo study all patients experienced the typical subjective symptoms (palpitation, fainting, weakness, epigastric distress) of the early dumping syndrome. During the glucose challenges with SMS 201-995 premedication three patients experienced nausea following the oral intake of glucose, but the characteristic signs of early dumping were absent. In the placebo study significant increases were detected (initial levels and maximum changes; mean (s.d.)) in the pulse rate (from 66 (8) to 102 (10) beats/min) in the packed cell volume (from 0·36 (0·05) to 0·43 (0·1) l/l) and in the plasma levels of VIP (from 3·0 (0·5) to 10 2 (1·8) pmol/l). During the somatostatin study there were no changes detected in these parameters. On the other hand there was a statistically significant difference in the changes of these parameters between the two glucose challenges ($P<0.001$, *Figure 1*). Blood glucose levels increased rapidly and reached their maximum value 30 min after the oral intake of glucose in the placebo study, while in the somatostatin analogue study the maximum was reached at 90 min. Hypoglycaemia developed in seven patients in the placebo study. During this period the blood glucose decreased from an initial level (mean (s.d.)) of 3·8 (0·8) to 1·8 (1·1) mmol/l. During the SMS 201-995 application no hypoglycaemia was detected. In the placebo study the insulin (from 10 (0·9) to 40 (9·1) µE/ml) and GIP levels (from 100 (13) to 220 (41) ng/l) showed a significant ($P<0.001$) elevation compared with the initial values, while in the somatostatin study the plasma insulin and GIP remained unchanged (*Figure 1*).

Discussion

The dumping syndrome following gastric surgery is a consequence of compensatory mechanisms. Rapid transit of

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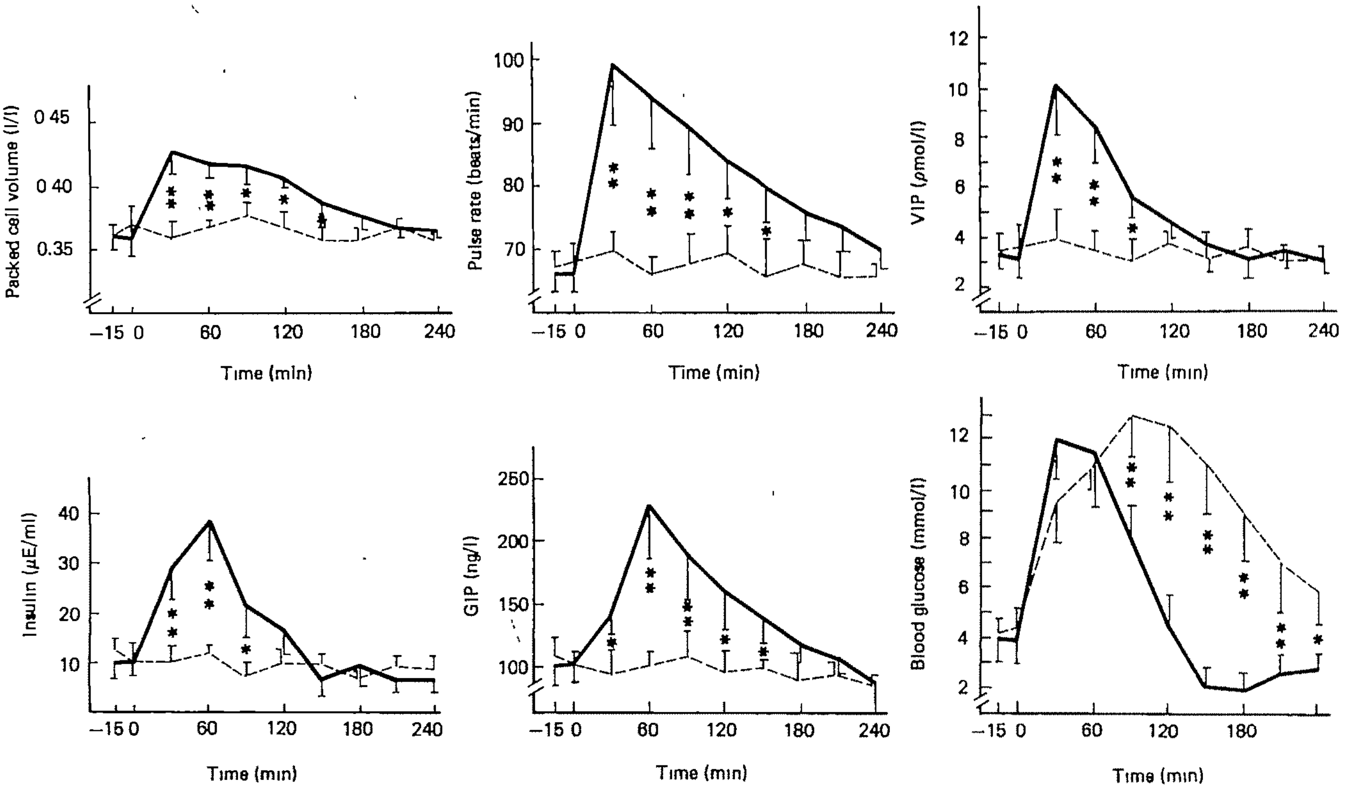

Figure 1 *Packed cell volume, pulse rate, vasoactive intestinal polypeptide (VIP), insulin, gastric inhibitory peptide (GIP) and blood glucose levels during glucose challenges with (---) and without (—) long acting somatostatin analogue SMS 201-995 (**$P<0.001$, *$P<0.01$)*

hyperosmolar food into the intestine causes a release of fluid and electrolytes into the upper small bowel. Simultaneously, haemoconcentration and the typical subjective symptoms of early dumping syndrome develop. During this process hormonal changes can also be observed; however, their primary role has not yet been established[1,2,3]. The elevation of VIP seems to be an important factor, because the infusion of VIP produces symptoms equivalent to the early dumping syndrome[2]. The main clinical feature of the late dumping syndrome is the reactive postprandial hypoglycaemia. It appears that the increased insulin release may in part be because of the relative hyperglycaemia and partly because of the increase in the GIP level.

The symptoms of the postprandial dumping syndrome seem to develop as a result of the release of various peptides. Somatostatin is a tetradecapeptide which inhibits the release of numerous gastrointestinal and pancreatic hormones, as well as inhibiting the secretion of fluid and electrolytes in the small intestine and increasing the gastrointestinal transit time[7]. These effects suggest that somatostatin might be beneficial in alleviating the signs of dumping syndrome. Previous studies are controversial[4,5,8].

Native cyclic somatostatin has a short half-life and therefore its clinical use is limited. Like native somatostatin SMS 201-995 suppresses the secretion of several regulatory peptides[7]; its effect is long acting. A previous study by Hopman *et al.* demonstrated that SMS 201-995 is effective in the prevention of clinical symptoms related to the dumping syndrome[9]. Hopman *et al.* studied only the changes in plasma insulin level and his results did not explain all the signs characteristic of this syndrome. In our study the hormonal changes provide a more detailed explanation of the beneficial effect of SMS 201-995 on the symptoms of the dumping syndrome. Our results demonstrate that the long acting somatostatin analogue alleviates not only the clinical signs of early dumping syndrome, but also inhibits the release of VIP This compound also blocks the increases in insulin and GIP which play a role in the development of postprandial hypoglycemia. Our study has shown that the long-acting somatostatin analogue SMS 201-995 has a beneficial effect in the prevention of both the subjective symptoms and the hormonal changes related to the early and late dumping syndrome following gastric surgery Therefore this compound might be of value in the management of the circulatory and metabolic disturbances associated with this syndrome.

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Biliary leakage and peritonitis following removal of T tubes after bile duct exploration

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After bile duct exploration for stones, it is common practice for surgeons to place a rubber T tube into the bile duct for a period usually of not less than 7 days. Farquharson recommends that 7–10 days should elapse before the tube is withdrawn[1]. The advantages claimed from this practice are firstly that it allows safe egress of bile in the event of a residual undetected bile duct stone obstruction and, secondly, that it enables postoperative T tube cholangiography to confirm clear ducts before T tube removal. The T tube forms a fistulous tract between the common bile duct and the skin, and when allowed to mature for 6 weeks even allows manipulation of a Burhenne catheter into the bile duct after removal of the tube. However, problems with T tubes can and do occasionally occur, and in a recent large review of surgical bile duct stones a 2·2 per cent complication rate was directly attributed to T tube drainage[2].

Safe removal of T tubes depends on the irritant properties of the T tube stimulating a reactive granulation track around the tube, thereby ensuring a temporary biliary cutaneous fistula which will normally close within a few days of T tube removal. It is noteworthy that 25 years ago the problem of bile duct leakage into the peritoneal cavity was reported following the introduction of a non-irritant, non-allergenic T tube made of polyvinyl chloride[3]. Winston *et al.* reported on four cases of biliary peritonitis with the use of polyvinyl chloride T tubes but cited references to 2000 explorations using latex rubber T tubes without this complication. The subsequent introduction of latex-based materials for T tube manufacture resolved this problem, and such material remains the most common composition for T tubes in use today. We report here, however, a disturbing series of 15 cases where the removal of a particular variety of T tube was followed by significant biliary leakage and peritonitis which required active intervention in 11 of 15 cases.

Case reports

Fifteen patients from five separate Scottish hospitals underwent elective cholecystectomy and exploration of the bile duct for stones (Victoria Infirmary, Glasgow: five cases, Ross Hall Hospital, Glasgow: two cases; Western Infirmary, Glasgow: five cases, Royal Alexandra Hospital, Paisley: one case; Ninewells Hospital, Dundee: two cases).

There were nine men and six women, and ages ranged from 22 to 70 years. In 14 cases a soft latex rubber T tube (Warne Franklin Surgical Products Ltd, High Wycombe, UK) was placed into the bile duct. In one patient there is doubt about which of two available varieties of T tube was used, but the possibility that a Warne T tube had been used could not be excluded. In every case, a postoperative T tube cholangiogram had confirmed that the bile duct was free from residual stones or other obstruction. Most of the T tubes were removed between 10 and 13 days after surgery (ten cases). The earliest T tube removal was at 7 days after operation and two patients had T tubes *in situ* for 20 days or more.

Ten patients developed acute generalized biliary peritonitis immediately after T tube removal and required urgent active intervention (laparotomy and drainage, eight cases; percutaneous catheter drainage, two cases). One of these patients required two separate laparotomies and one required percutaneous drainage during a hospital stay of 43 days.

One patient was readmitted with biliary peritonitis 2 weeks after hospital discharge following T tube removal and required percutaneous drainage on two separate occasions for a large subhepatic bile collection.

Four patients who developed localized peritonitis immediately after T tube removal were treated conservatively with intravenous fluids and antibiotics, although one of these patients suffered septicaemia. All patients survived. The inpatient hospital stay ranged from 18 to 45 days (average 27 days).

Discussion

The unexpected cluster of cases of biliary peritonitis after T tube removal raised questions of common factors in aetiology. Seven cases encountered at the Victoria Infirmary, Glasgow and Ross Hall Hospital, Glasgow, occurred within a period of a few months and it was quickly established that the T tube used had been manufactured by Warne Franklin Surgical Products Ltd.

Preliminary enquiry revealed that in September 1986 the specification of urinary catheters and tubes had been changed. The company had developed a new non-allergenic, non-irritant latex which was used to manufacture their Foley catheters, and the process had been extended to include their T tubes. At this time the two cases reported here from Ninewells Hospital, Dundee, led to a surgical decision to remove Warne tubes from their storage shelves, since which time no further misadventures have occurred in that department. It was around this time that Warne Franklin Surgical Products Ltd. apparently stopped T tube manufacture. However, large stocks of these T tubes remained available for use, and following a cluster of cases at the Western Infirmary, Glasgow, one of the surgeons altered his practice in favour of direct bile duct closure without drainage.

That substantial stocks of Warne T tubes may remain in many hospitals seems likely, and is reflected by cases reported here from five separate hospitals.

While it is accepted that sporadic mishap may follow the use of any variety of T tube, a recent survey[4] on the use of T tubes after common bile duct exploration calculated the risk of biliary peritonitis each time a T tube is removed to be of the order of 0·84 per cent, or one in every 119 explorations. This incidence of bile leakage seems much higher than previously reported experience[3]. It is not clear in the study by Corbett *et al.*[4] which manufacturer's T tube was used. Our observations raise the question of whether a preponderance of non-allergenic T tubes in that report may account for the high incidence of bile leak. The cluster of cases reported here, where T tubes from Warne Franklin Surgical Products Ltd. were certainly used in 14 cases, suggests strongly that the original search for a non-irritant, non-allergenic tube has proved so successful that bile T tubes manufactured by the company have failed to allow mature T tube tracks to form. Nevertheless, no information on the likelihood of such mishaps has so far reached Regional Health Boards. We therefore recommend that surgeons remove Warne T tubes from their shelves.

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Case report

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Compartment syndrome: a cautionary tale

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Compartment syndrome is a condition in which increased tissue pressure within a closed anatomical space reduces capillary perfusion sufficiently to compromise viability of the enclosed tissues. The acute syndrome is most commonly post-traumatic, but rarely complicates operative positioning of patients. We report a case of bilateral lower limb compartment syndrome occurring after surgery with a patient in the lithotomy position in Lloyd–Davies supports.

Case report

A 26-year-old 60 kg man who had 6 months previously undergone total colectomy for fulminating ulcerative colitis was admitted for restorative proctectomy. All preoperative investigations were normal. The patient was positioned in Lloyd–Davies supports to the satisfaction of both surgeons. The procedure took 4 h with the table positioned head-down for 2 h. There were no surgical complications. The patient was hypotensive with a systolic blood pressure of 80 mmHg for the first half of the procedure.

When reviewed 4 h postoperatively the patient complained of pain in both calves. On examination both were swollen, with prominent superficial veins. He had good peripheral pulses and capillary return, and sensation was normal to light touch in both legs. There was no increase in pain on passive movement of feet or toes. Examination by Doppler ultrasonography showed good arterial and deep venous flow. Treatment was symptomatic.

The next morning his pain had lessened but signs were unchanged. By midday, he had altered skin sensation overlying the lateral compartments of both legs, and a right foot drop. A diagnosis of bilateral compartment syndrome was made and he underwent emergency bilateral four-compartment fasciotomy.

At operation, all compartments in both legs were affected with doubtful muscle viability in the right anterior and peroneal compartments, which was confirmed at a second procedure when some necrotic muscle had to be excised.

The fasciotomy wounds were allowed to heal by second intention and the patient made a good functional recovery although he had some weakness of dorsiflexion of the right ankle and altered sensation in the distribution of the right deep peroneal nerve.

Discussion

The diagnosis of compartment syndrome should not be missed or delayed. The early symptoms are due to reduced perfusion of nerve and muscle cells and classically include pain out of proportion to physical findings, a tense compartment, paraesthesiae in the distribution of nerves running through the compartment, and muscle weakness with pain on passive stretching. Peripheral pulses are unchanged until late in the process when intracompartmental pressure approaches the diastolic pressure. A diagnosis of compartment syndrome was entertained on the evening of surgery but was considered unlikely in view of the lack of neurological signs. The operative time seemed insufficiently long to support such a diagnosis.

Bilateral lower limb compartment syndromes have previously been reported in patients undergoing prolonged operation in the lithotomy position[1–3] but we are unaware of its having occurred after a 4 h procedure in this position. Patients in the lithotomy position are at risk from decreased lower limb perfusion through two mechanisms: first by compression against supports, and secondly from elevation of the limb above heart level, reducing perfusion pressures. In our patient, two other factors were probably of importance: first the initial 2 h of hypotension and, second, his having well developed muscles (he was a keen oarsman), allowing little room for expansion within compartments.

Our patient suffered unfortunate muscle loss from delay in diagnosis due to our ignorance of this hazard and our consequent disbelief in the possibility until the physical signs were advanced. Earlier diagnosis and fasciotomy would have saved him from some disability. Awareness of this possibility by surgeons operating in young fit patients in prolonged lithotomy, and early action, will prevent such catastrophic consequences.

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Gastrocolic fistula as a complication of benign gastric ulcer: report of four cases and update of the literature

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Four cases of gastrocolic fistula complicating benign gastric ulcer are described, bringing the total number of individually reviewed cases in the English language literature to 108. A review of 30 cases reported in the past 10 years reveals a surprisingly high percentage of young, female patients. Three-quarters of these patients used steroidal or nonsteroidal anti-inflammatory agents. The presence of such fistulae is suspected in patients complaining of weight loss, diarrhoea and faecal vomiting. Small fistulae may not be suspected when overshadowed by other complications of ulcer disease such as bleeding or perforated viscus. Medical management of benign gastrocolic fistulae may be indicated in some circumstances. Surgical treatment involves en bloc *resection, including the fistula, and surrounding colon and gastric segments.*

Keywords: Gastric ulcer, gastrocolic fistula

Gastrocolic fistula is a well-recognized complication of malignancies arising from the stomach or colon, and of surgery performed for benign disease of these organs[1–6]. Such fistulae arise rarely as complications of benign peptic ulcer of the stomach. We report four new cases of this complication, including one which presented with upper gastrointestinal haemorrhage before the fistula had become clinically apparent. In addition, we review 30 cases (including the four reported here) which have been described since the comprehensive review of this topic by Madsen *et al.*[6] 10 years ago. This review emphasizes that gastrocolic fistulae complicating benign gastric ulcer arise in close association with intake of steroidal and nonsteroidal anti-inflammatory agents. Some of these lesions may be amenable to medical management. Surgery is required in cases presenting with persistent physiological disturbance or those complicated by haemorrhage or perforation of a viscus.

Case report 1

A 62-year-old Caucasian man was admitted to the University of Utah Medical Center with a 1-year history of gastric ulcer. He had been intermittently compliant with medication regimens which included antacids and cimetidine. Two months before admission, his epigastric pain worsened and he experienced frequent episodes of nausea, vomiting, and watery diarrhoea, associated with a weight loss of 30 lb. He smoked approximately ten cigarettes per day and drank alcohol rarely. He had not ingested steroids, aspirin or other nonsteroidal anti-inflammatory agents. He had not previously required abdominal surgery. An abdominal computed tomography (CT) scan revealed a 6-cm infrarenal abdominal aortic aneurysm. Laboratory data on admission were normal. Upper and lower gastrointestinal radiographs demonstrated a communication between the posterior lesser curve of the stomach and the colon just proximal to the splenic flexure (*Figure 1*). At surgery, a truncal vagotomy was performed in conjunction with *en bloc* removal of the gastric antrum, the fistulous tract and a segment of transverse colon. Primary gastroduodenal and transverse colonic anastomoses were performed. Microscopic examination of the specimen revealed no evidence of malignancy. The patient recovered uneventfully and 4 weeks later underwent repair of his abdominal aortic aneurysm.

Case report 2

A 76-year-old Caucasian man was admitted to the Salt Lake City Veterans Administration Medical Center with a 2-day history of epigastric pain and faecal vomiting. His past medical problems included a long history of rheumatoid arthritis, for which he had been receiving oral steroid and nonsteroid anti-inflammatory agents. Smoking and alcohol abuse histories were not available. Physical examination

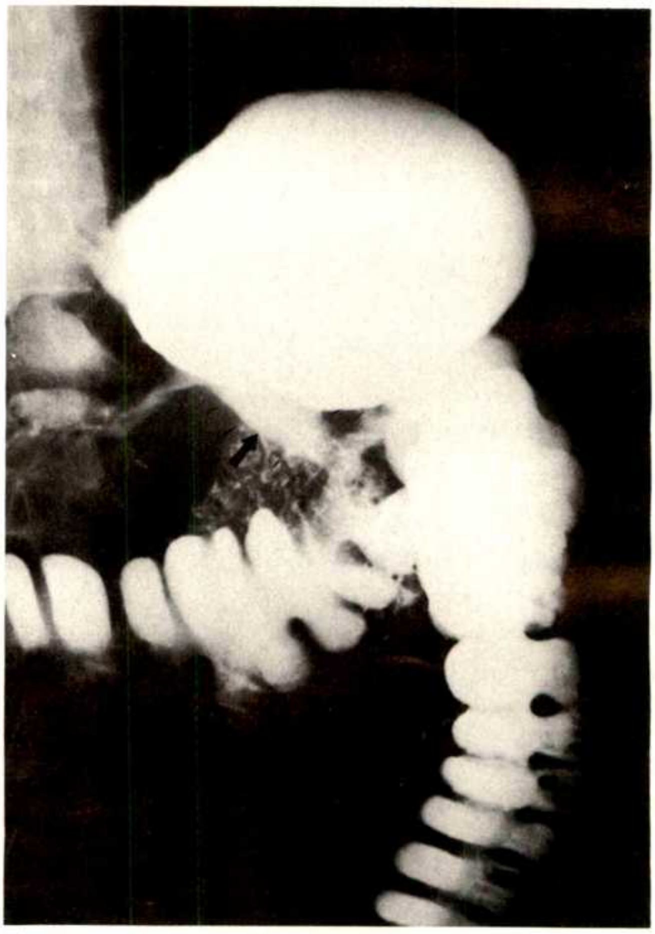

Figure 1 *A barium enema was performed in this patient (Case report 1), demonstrating a fistulous tract between the gastric antrum and the medial aspect of the splenic flexure of the colon*

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revealed dehydration, malnutrition and guaiac-negative stool. Barium enema demonstrated a fistulous communication between the greater curvature of the stomach and the transverse colon just proximal to the splenic flexure. Gastroscopy revealed a 4 × 2 cm opening to the fistula which failed to heal after 5 weeks of management with bowel rest and parenteral nutrition. At operation, the duodenum and a loop of jejunum were adherent to the phlegmon but did not communicate with the fistula. An *en bloc* 75 per cent gastrectomy with segmental colonic resection was performed. A Roux-en-Y gastrojejunostomy was constructed and the two ends of the transverse colon were brought out as separate colostomies to the skin. The patient died on the fifth postoperative day owing to sepsis and multiple organ failure

Case report 3

A 66-year-old Caucasian woman was admitted to the John Cochran Veterans Administration Medical Center of St. Louis with a 10-day history of epigastric pain and melaena. In the past 20 years, she had intermittently taken antacids and H$_2$-receptor antagonists for a duodenal ulcer. In the past 5 years, she had ingested daily amounts of twenty to thirty 325 mg tablets of aspirin and four 600 mg tablets of ibuprofen for exacerbations of arthritis. She had smoked up to two packs of cigarettes per day for 40 years but had no history of alcohol or steroid use. Physical examination was remarkable for epigastric tenderness and melaenic stool. Admission laboratory data included a haemoglobin of 8·2 g/dl and a white blood cell count of 13·1 cells/mm^3 but were otherwise normal. Barium meal and upper gastrointestinal endoscopy revealed only a deep 2 cm ulcer crater on the dependent portion of the posterior greater curvature of the stomach

After admission, bleeding per rectum recurred and she required a transfusion of 6 units of blood. After bowel preparation, she underwent laparotomy. The greater curve of the antrum and distal corpus of the stomach were found to be adherent to the distal transverse colon. A 60 per cent gastrectomy and segmental transverse colectomy were performed, with truncal vagotomy, gastroduodenal anastomosis and primary transverse colon reanastomosis. Examination of the specimen revealed a fistulous communication between the stomach and resected transverse colon segment. No malignancy was identified in the specimen. The patient was discharged 2 weeks after operation, doing well.

Case report 4

A 34-year-old Caucasian woman was admitted to Barnes Hospital with a 12 to16 month history of watery diarrhoea. In the 6 months before admission, she experienced daily episodes of abdominal cramping, foul eructation, vomiting and, on occasion, stools containing red blood. For the previous 8 years she had been taking cimetidine for epigastric pain. A gastric ulcer had been documented 18 months previously by barium examination at another hospital She had smoked one pack of cigarettes per day since adolescence and ingested ten 325 mg aspirin tablets per day for headaches. She drank alcohol occasionally. Physical examination revealed a thin, dehydrated and pale young woman. The abdomen was not tender and the stool was guaiac-negative. Laboratory studies were not remarkable, except for a serum K$^+$ of 2·1 mmol/l. A serum gastrin level was elevated at 500 pg/ml. A gastrocolic fistula was demonstrated by barium meal examination and at endoscopy, communicating between the anterior aspect of the lesser curve of the stomach and transverse colon. The patient subsequently underwent *en bloc* resection of the fistula, distal two-thirds of the stomach and a segment of the transverse colon. A gastroduodenal anastomosis and primary reanastomosis of the transverse colon were performed. Histological examination of the specimen revealed no evidence of malignancy. Postoperative serum gastrin levels were undetectable. The patient was discharged 2 weeks after operation, doing well.

Discussion

In 1755, Haller described a case of gastrocolic fistula associated with abdominal cancer[1]. In 1897, Bec identified 62 such fistulae, 12 due to gastric ulcer[2]. In 1920, Firth reported the first case in the English language literature of gastrocolic fistula secondary to benign gastric ulcer[3]. A number of disease processes have been associated with gastrocolic fistula, including carcinomas and lymphomas of the stomach or colon, colonic diverticulitis, tuberculosis, syphilis, mycosis or inflammatory bowel disease[4–6]. In addition, such fistulae have been recognized as complications of surgical procedures of the stomach, distal transverse colon and splenic flexure[4–6].

As complications of benign gastric ulcer, such fistulae are uncommon. Akwari *et al.*[5] found four cases of this complication in reviewing a 10 year experience in which 957 patients underwent operation for benign gastric ulcer and its complications. Expanding on the work of Cody *et al.*[4] and Akwari *et al.*[5], Madsen *et al.* identified 77 cases of this complication, and added one of their own[6]. Since Madsen's review, 30 individually discussed cases (including the four reported here) were identified in English language journals[7–24]. It therefore seemed appropriate to update the discussion of the presentation and management of these fistulae, based on the cases reported in the past decade since the review of Madsen *et al.*[6].

Table 1 summarizes some of the presenting characteristics of these 30 patients. Two-thirds of these patients were female, in contrast to the nearly equal proportion of men to women in the cases collected by Madsen *et al.*[6] In addition, 11 of the patients were aged 50 or under, and ten of these were women. Approximately three-quarters of patients, in whom the history was available, were ingesting oral preparations of steroidal or nonsteroidal anti-inflammatory agents. Less than one-half of these patients gave a previous history of peptic ulcer or dyspeptic symptoms. Alcohol consumption and tobacco use were not uniformly recorded. Of the four patients described in the present report, three were currently smoking cigarettes and none had a history of alcohol abuse.

Table 2 summarizes the symptoms with which these 30 patients presented. As recorded previously[4–6], the most frequent symptoms included diarrhoea, weight loss, faecal vomiting and epigastric pain. Bleeding, manifested as haematemesis, melaena or haematochezia, was recorded in less than one-third of cases. Two cases[18,19] presented with perforation of the colon into the peritoneum. In almost 80 per cent of these cases, patients sought medical attention within 3 months of the onset of symptoms Thus, classically, gastrocolic fistulae are diagnosed in patients with faecal vomiting, but may be suspected in patients with unexplained abdominal pain, diarrhoea and a history of heavy ingestion of nonsteroidal or steroidal anti-inflammatory agents. Absence of previous peptic ulcer disease does not exclude the diagnosis.

The diagnostic studies routinely used in evaluating these lesions have included barium meal, gastroscopy, and barium enema. In six of 20 cases where it was used for diagnosis, the barium meal examination failed to document such fistulae.

Table 1 *Presenting characteristics of 30 reported cases of benign gastrocolic fistula from 1978 to 1988*

Male:female ratio	10:20
Mean age at presentation	
Males	61 years (range 46–77 years)
Females	52 years (range 26–80 years)
Previous history of ulcer disease/symptoms	15/29 patients (one patient was not recorded)
Ongoing use of steroids or NSAIDS (aspirin, motrin, indocin, naproxen)	18/24 patients (one patient used unidentified analgesics; five patients were not recorded)

NSAIDS, non-steroidal anti-inflammatory drugs

Table 2 *Presenting symptoms of 30 reported cases of benign gastrocolic fistula from 1978 to 1988*

	n	%
Weight loss	20	67
Onset or acute change in epigastric pain	19	63
Diarrhoea	19	63
Faecal vomiting	14	47
Melaena or haematochezia	8	27
Halitosis	6	20
Colonic perforation	2	7

Similarly, upper gastro-intestinal endoscopy failed to document evidence of fistula in five of 19 cases where it was performed for diagnosis as well as for biopsy of the lesion. In the 15 cases where it was used for diagnosis, however, barium enema detected the presence of gastrocolic fistula, even when the barium meal and gastroscopy had failed. Here in Case report 3, it seems likely that colonoscopy would have visualized the erythematous area surrounding the colonic mucosal end of the fistula. Barium enema or colonoscopy may thus be the most sensitive studies in visualizing these fistulae; nevertheless, gastroscopy with multiple biopsies of the ulcerated gastric aspect should be performed to exclude the presence of carcinoma in such lesions.

Since these lesions remain quite rare, the optimal approach to their management remains unresolved. Ekbom and Liedberg[16] and McCullough and Gregson[20], after carefully documenting the absence of malignancy in the fistula, treated their patients successfully with oral H_2-antagonists and by discontinuing ulcerogenic medications. No recurrences were observed in short-term follow-up Thus, rapid response to nonoperative measures may suggest that the patient's fistula and ulcer will heal without operation. When malignancy has been reliably excluded, expectant management may be warranted.

In 27 of the patients summarized here, operative approaches included excision of the fistulous tract locally (4 cases), or excision of the fistula with segmental colon resection and resection of the stomach including and distal to the fistula. In 16 patients, it was possible to reconstruct the upper tract with a Billroth I gastroduodenostomy emphasizing the absence of duodenal involvement in many of these inflammatory processes. In seven patients it was necessary to reconstruct with a gastrojejunostomy. Two perioperative deaths were recorded (Case report 2, the present report and Reference 22) among these 27 patients. Preoperative parenteral nutrition, bowel rest, use of intravenous H_2-receptor antagonists, and mechanical bowel preparations have been helpful in preparing patients for surgery and reducing morbidity of surgery for these lesions. To exclude malignancy in these lesions, it is necessary to excise the fistula, surrounding stomach and involved colon *en bloc*. Frozen sections of the fistulous tract should be submitted to exclude the possibility of malignancy.

One final issue in the management of these patients is illustrated by the recurrence of benign gastrocolic fistula recorded by Hollingshead *et al.*[13]. Their patient had uneventful recovery following surgery, but developed recurrence of a fistula 8 months later after resuming naproxen to control his severe arthritis. Perrault *et al.*[25] recently called attention to a subgroup of patients who presented with chronic recurrent gastroduodenal ulcers which ultimately failed to respond to medical management. Of the 4 patients described, three were young women, and all were under the age of 43. Ultimately, these patients were identified as surreptitious salicylate abusers. In view of the high rate of usage of steroidal or nonsteroidal anti-inflammatory agents in patients with gastrocolic fistulae, it may be prudent to monitor use of these medicines and perhaps measure salicylate levels in follow-up of some of these patients.

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Time-related changes in characteristics of prognostic significance in carcinomas of the oesophagus and cardia

During 25 years (1960–84) 657 patients were operated on for squamous cell carcinomas ($n=230$)*, adenocarcinomas* ($n=399$) *or anaplastic carcinomas* ($n=28$) *of the thoracic oesophagus or cardia. The male:female ratio was 2·8:1 and the mean age was 66 years (range 22–91 years). Oesophagogastrectomy* ($n=514$) *was performed whenever technically possible. From the first (1960–64) to the last (1980–84) 5-year period the proportion of adenocarcinomas increased from 56 to 78 per cent* ($P<0{\cdot}001$)*, poorly differentiated cancers increased from 34 to 65 per cent* ($P<0{\cdot}0001$)*, and stage III–IV tumours increased from 72 to 88 per cent* ($P<0{\cdot}05$)*. Five-year cumulative rates(s.e.) were 11(3) per cent for operations during 1960–69* ($n=262$)*, 8(2) per cent during 1970–79* ($n=256$) *and 3(2) per cent during 1980–84* ($n=139$; $P<0{\cdot}05$)*. Hospital mortality rates (≤30 days) and 5-year cumulative survival rates(s.e.) were 6·5 per cent and 36(7) per cent* ($n=46$) *for stage I, 14·0 per cent and 21(4) per cent* ($n=114$) *for stage II, 17·8 per cent and 5(1) per cent* ($n=258$) *for stage III and 23·8 per cent and 3(1) per cent* ($n=239$) *for stage IV tumours* ($P<0{\cdot}05$ *and* $P<0{\cdot}001$)*. Well differentiated* ($n=70$) *cancers, those of medium differentiation* ($n=239$) *and poorly differentiated cancers* ($n=348$) *had 5-year survival rates(s.e.) of 24(5), 10(2) and 5(1) per cent, respectively* ($P=0{\cdot}0007$)*. Squamous cell carcinomas had a better prognosis than adenocarcinomas, even after stratification according to location of primary tumour. The 657 patients who underwent surgery constituted 50 per cent of a total of 1316 cases with cancer of the oesophagus and cardia reported from our catchment area during the study period. Frequency of surgery decreased with age. The annual incidence (number per 100 000 inhabitants aged 20 years or more) of adenocarcinomas of the lower oesophagus and cardia doubled to 5·9 in 1980–84, while that of squamous cell carcinomas tended to decrease (to 2·9). A successive worsening of long-term survival after surgery was explained by significant changes in cancer characteristics having pronounced prognostic significance. Over the 25 years the carcinomas changed towards the present pattern where poorly differentiated adenocarcinomas of the lower third of the oesophagus and cardia in stages III–IV have become predominant.*

Keywords: Carcinomas, oesophagus, cardia, surgical treatment, long-term survival, altered cancer characteristics

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Patients with carcinomas of the thoracic oesophagus or cardia usually have advanced disease at the time of diagnosis[1,2]. Symptoms are non-specific but invariably present, and a mean weight loss of 10 kg is the rule[2]. The disease is most prevalent late in life and it is not surprising that prognosis has remained poor during the past 30 years[2,3]. In the absence of a major therapeutic breakthrough, oesophagogastrectomy remains the treatment of choice.

Using Cox's regression analysis a detailed risk estimation was previously performed on 657 patients operated on over a 25-year period[4]. A rather discouraging observation, which has not previously been reported, was made: namely that prognosis after surgery worsened progressively during the 25-year period. Since the operative year had no independent prognostic influence[4], the explanation should, in theory, be sought in time-related alterations in cancer characteristics. A clue was given by the fact that the annual incidence of cancers of the cardia in Denmark has shown a steady increase since the 1950s, while that of oesophageal cancers has shown a slight decrease[5].

The aim of the present report was to pinpoint possible changes in cancer characteristics during the 25-year period and to relate such changes to the postsurgical worsening of prognosis. Furthermore, this surgical series was compared with the background material which included 1316 cases with cancer of the oesophagus or cardia reported from our catchment area during the study period.

Patients and methods

Carcinomas

A total of 657 patients were operated on for carcinomas of the thoracic oesophagus or cardia from 1960 to 1984. Until recently the policy was to explore all patients, to resect the cancer whenever technically possible and to intubate (Celestin® tubes, Medoc, Gloucester, UK) the rest intraoperatively.

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Operation was denied to only 45 patients during the study period. These patients are not included in the information presented here. The male:female ratio was 2·8:1, and the mean age was 66 years (range 22–91 years). Before operation, 615 patients had varying degrees of dysphagia, and 587 had experienced weight loss ranging from 1 to 35 kg (mean 10 kg). All patients had upper gastrointestinal symptoms. The patients have been described in detail previously[4].

Radiographs of the oseophagus (barium swallow) and oesophagogastroscopy with biopsy of the tumour were performed in all patients. Staging of the disease was mainly based on intraoperative TNM (tumour node metastasis) classification[6], including macroscopic and histological examination of the surgical specimens: stage I, $T_1N_0M_0$, stage II, $T_2N_0M_0$; stage III, $T_{1-2}N_1M_0$ or $T_3N_{0-1}M_0$; and stage IV, $T_{1-3}N_2M_0$ or $T_{1-3}N_{0-2}M_1$. The tumour locations were divided into four (oesophagus parts I–III, and cardia) as depicted in *Figure 1*. Location of the bulk of the tumour was used to discriminate between oesophagus part III and cardia in the case of extension between the two sites. There were 230 squamous cell carcinomas, 399 adenocarcinomas, and 28 anaplastic carcinomas (*Figure 1*).

Operative technique

The surgical technique has been described in detail previously[4,7]. In short, *en bloc* oesophagogastrectomy followed by careful mobilization of the stomach and intrathoracic end-to-end oesophagogastrostomy with deep oesophageal invagination was performed whenever possible ($n=481$). Roux-en-Y oesophagojejunostomy ($n=21$) was used after total gastrectomy and colon interposition ($n=12$) was performed when the stomach could not be sufficiently mobilized. Splenectomy was performed in 483 patients. Associated surgical procedures (stage III or IV exclusively) included liver resection ($n=2$), pancreatic resection ($n=27$), transverse colonic resection ($n=3$), adrenalectomy ($n=2$), pulmonary lobectomy ($n=6$), pulmonary subsegmental resection ($n=6$), tracheal resection ($n=4$) and diaphragmatic resection ($n=6$).

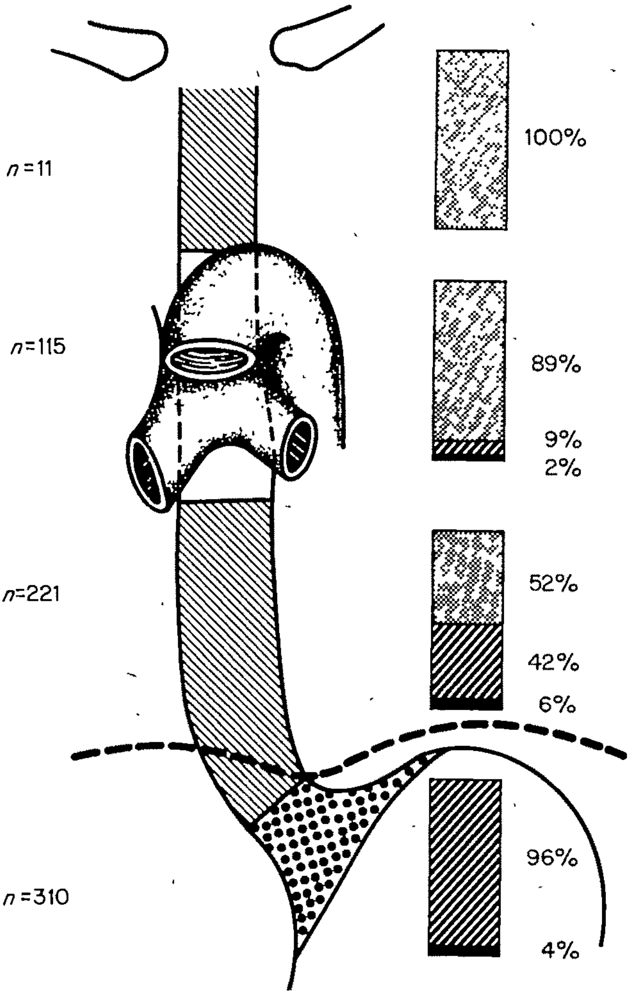

Figure 1 *Histological diagnosis in relation to location (surgical material). Thoracic inlet (indicated by the tips of the clavicles), upper margin of aortic arch, lower border of right main bronchus, and oesophagogastric junction separate location of the tumours into thoracic oesophagus parts I to III and cardia as indicated. The number of patients and percentage of the different histological types are given for each location. The distribution of histological types differed significantly between the locations* (P<0·0001). *Shadings represent* □, *squamous cell carcinoma;* ▨, *adenocarcinoma; and* ■ *anaplastic carcinoma*

Follow-up

In November 1986, 30 patients were alive from 1·8 to 24 years after the operation. Death certificates were available for all 627 deaths and autopsy reports for 306.

Background material

Since 1943 the Danish Cancer Registry has registered newly diagnosed cases of cancer in Denmark[8]. Data for all cases with cancers of the oesophagus and cardia reported from our catchment area during the study period (1960–84) were put at the authors' disposal by the Danish Cancer Registry, Institute of Cancer Epidemiology (Danish Cancer Society, Copenhagen). The tumours were classified according to the ICD-7 (International Classification of Diseases, WHO) code[9] before 1978 when the ICD-0 code[10], which includes detailed topographic and morphological information, was put into use. For the sake of continuity, the ICD-0 was translated into the ICD-7 system for the present study ICD-7 coding primarily infers that adenocarcinomas of the oesophagus, especially of the lower third, were classified as cardia tumours.

Statistical analysis

Comparisons between groups were performed using the standard χ^2 test or the one-way analysis of variance whenever appropriate. Cumulative survival rates were estimated using the Kaplan–Meier method and differences between curves judged with the log rank test and the Gehan (generalized Wilcoxon) test. All tests were computerized using the BMDP statistical package (BioMedical Data Processing Incorporated, Los Angeles, California, USA)[11]. The level of significance was chosen as 0·05. Quantitative data are given as mean(s.d.) or mean(s.e.m.). Cumulative survival estimates are given together with their standard error (s.e.)

Results

The histological types of the tumours are shown in *Figure 1* relative to location. The degree of histological differentiation was judged to be high in 11 per cent ($n=70$), medium in 36 per cent ($n=239$) and low in 53 per cent ($n=348$) of cases, without differences between squamous cell carcinomas and adenocarcinomas. Women ($n=171$) had squamous cell carcinomas in 52 per cent of cases, adenocarcinomas in 43 per cent of cases, and anaplastic carcinomas in 5 per cent of cases, compared with 29, 67, and 4 per cent, respectively, for men ($n=486$; $P<0·0001$).

The characteristics of the cancers changed throughout the study period, as shown in *Figure 2*. The fraction of patients with adenocarcinomas increased from 56 per cent in 1960–64 to 78 per cent in 1980–84, which was paralleled by an increase in the number of cardia tumours. Poorly-differentiated carcinomas showed a highly significant increase from 34 per cent in the first 5-year period to 65 per cent in the last; this was reflected by a rise in the fraction of patients with stage III or IV disease to 88 per cent in 1980–84. The mean(s.d.) duration of symptoms before diagnosis (6(4) months), the mean(s.d.) diameter of primary tumour mass (6·4(3·4) cm), and the sex and age distributions did not differ between the periods shown in *Figure 2*.

Resection of the tumour was accomplished in 514 patients (78 per cent) and was macroscopically radical in 368. The hospital mortality rate (≤30 days) was 19 per cent and the 5-year cumulative survival rate(s.e.) was 9(1) per cent. Overall long-term prognosis worsened during the period of study (*Table 1*), despite a decrease in hospital mortality (21 per cent for 1960–69, 18 per cent for 1970–79, and 15 per cent for 1980–84; not significantly different). The stage of the tumour was a strong predictor of long-term survival (*Figure 3*), with 5-year survival rates(s.e.) of 36(7) per cent for stage I, 21(4) per cent for stage II, 5(1) per cent for stage III and 3(1) per cent for stage IV ($P<0·0001$). Hospital mortality rate was 6·5 per cent ($n=3$), 14·0 per cent ($n=16$), 17·8 per cent ($n=46$) and 23·8 per cent, respectively, for stages

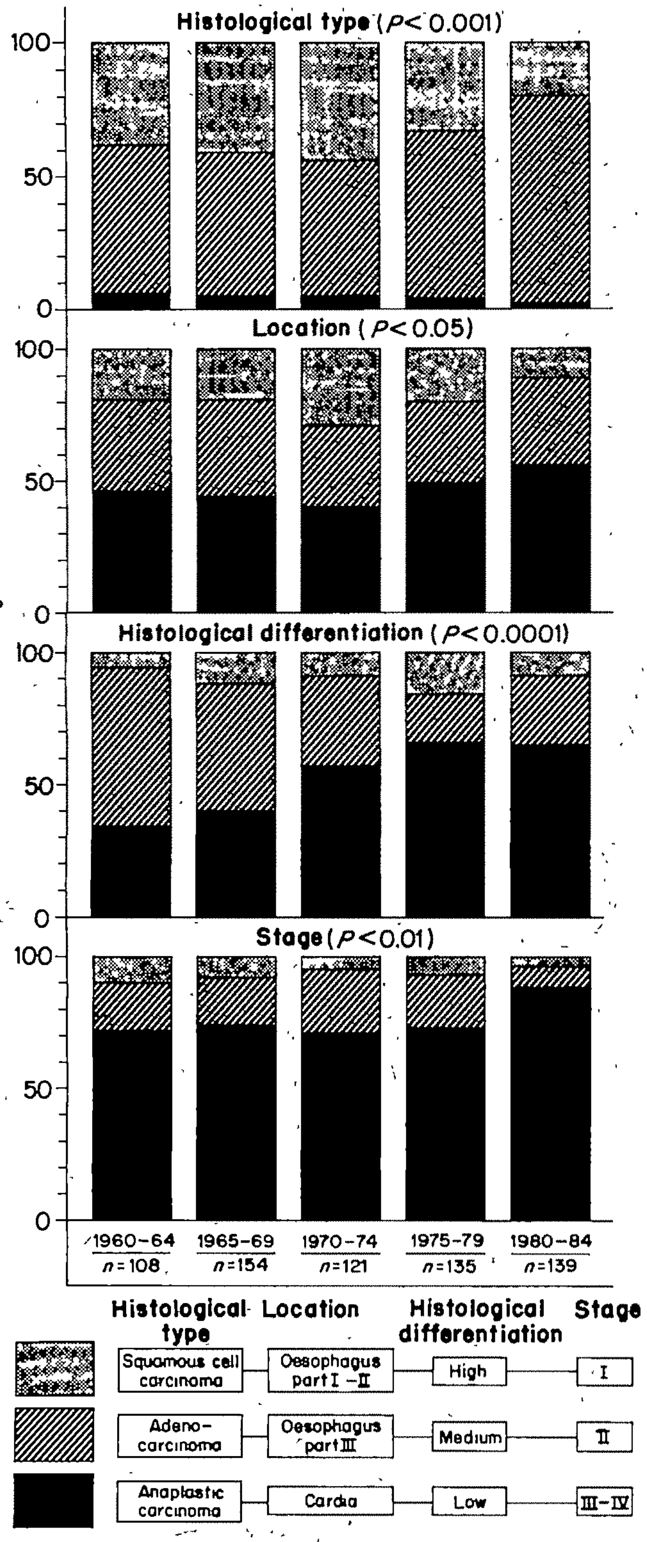

Figure 2 *Changes in cancer characteristics in relation to the five 5-year periods included in the present study (surgical material). Each modality (histological type, location, etc.) is divided into three subgroups with shadings as indicated*

I to IV ($P<0{\cdot}05$). Other important correlates of long-term survival are given in *Table 1*. Histological differentiation by itself exerted a pronounced prognostic influence with mean(s.e.m.) 5-year survival rates ranging from 24 per cent for well differentiated cancers to 5 per cent for poorly differentiated cancers. *Table 2* shows various characteristics of squamous cell carcinomas and adenocarcinomas separated according to location. T_3 tumours were most prevalent in squamous cell carcinomas of the first two parts of the oesophagus, while adenocarcinomas of the cardia had the highest frequency of organ metastases (M_1 class) and the largest tumour diameters. Adenocarcinomas of the oesophagus had an extremely bad prognosis compared with cardia tumours, while squamous cell carcinomas of the third part of the oesophagus had a better prognosis than those of the first and second parts. The fraction of patients who had a radical resection did not differ between the five groups of patients in *Table 2*.

The background material including 1316 cases is outlined in *Table 3* for the year of diagnosis (and operation). The annual incidence of oesophageal cancers showed a decreasing tendency during the study period while that of cardia cancers doubled. In total almost, 50 per cent (equivalent to the present surgical series) were operated on (*Table 3*). The frequency of surgery

Table 1 *Factors affecting long-term survival in 657 patients operated on for carcinoma of the thoracic oesophagus or cardia*

Factor	Number of patients	Percentage 5-year cumulative survival rate (s.e.)	*P*
Year of operation			
1960–69	262	11 (3)	
1970–79	256	8 (2)	0·04
1980–84	139	3 (2)	
Histological type			
Squamous cell carcinoma	230	11 (2)	
Adenocarcinoma	399	8 (1)	0·02
Anaplastic carcinoma	28	0	
Location			
Oesophagus parts I–II	126	7 (2)	
Oesophagus part III	221	9 (2)	0·004
Cardia	310	9 (2)	
Histological differentiation			
High	70	24 (5)	
Medium	239	10 (2)	0·0007
Low	348	5 (1)	
Diameter of primary tumour mass (cm)			
≤3·0	114	15 (3)	
3·1–6·0	272	8 (2)	0·0001
6·1–9·0	149	7 (2)	
≥9·1	122	5 (3)	
Age (years)			
≤55	103	10 (3)	
56–65	180	12 (2)	0·0001
66–75	241	9 (2)	
≥76	133	3 (2)	

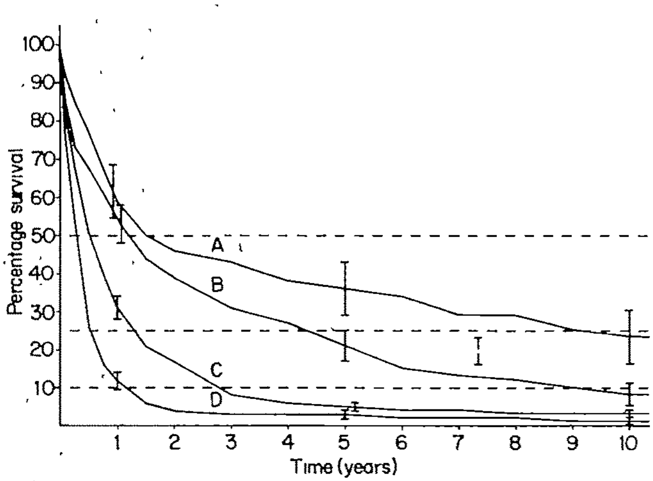

Figure 3 *Cumulative survival in relation to stage (surgical material) for: A, stage I (n=46), B, stage II (n=114), C, stage III (n=258); and D, stage IV (n=239) Standard error for each curve is shown at 1, 5 and 10 years. The curves differed significantly ($P<0{\cdot}0001$)*

Table 2 *Characteristics of squamous cell carcinomas and adenocarcinomas in relation to location in surgical patients*

	Oesophagus parts I+II		Oesophagus part III		Cardia	P value
	SQCC	ADC	SQCC	ADC	ADC	
n	114	10	116	91	298	
Medium/low differentiation (%)	49/45	50/50	37/48	31/59	39/52	n.s.
T_3 tumour (%)	46	20	29	18	24	<0·0001
N_1/N_2 classification* (%)	29/27	50/20	30/30	45/27	35/33	n.s.
M_1 classification (%)	7	0	16	12	21	<0·01
Stage III or IV (%)	75	80	70	76	77	n.s.
Mean (s.d.) diameter of primary tumour mass (cm)	5·7 (2·9)	5·3 (2·2)	5·9 (3·0)	5·8 (3·0)	7·0 (3·6)	<0·01
Mean (s.d.) age (years)	66 (11)	69 (15)	68 (9)	67 (10)	66 (11)	n.s.
Percentage 5-year cumulative survival rate (s.e.)	8 (3)	0	13 (3)	2 (1)	9 (2)	<0·05

SQCC, squamous cell carcinoma; ADC, adenocarcinoma, * N_1 class precluded N_2 class but not *vice versa*; n.s., not significant

Table 3 *Details of all cases with cancers of the oesophagus and cardia reported to the Danish Cancer Registry from our catchment area and of the 657 patients with carcinomas who were operated upon (present surgical patients) in relation to year of diagnosis/operation.*

	1960–64	1965–69	1970–74	1975–79	1980–84	1960–84
All reported cases						
Oesophagus* (annual incidence†)	159 (3·6)	168 (3·6)	92 (2·7)	105 (2·9)	110 (2·9)	634
Cardia* (annual incidence†)	101 (2·8)	152 (3·9)	114 (4·4)	140 (5·1)	175 (5·9)	682
Total	260	320	206	245	285	1316
Present surgical cases						
Oesophagus‡ (percentage of reported cases)	58 (36)	86 (52)	73 (79)	69 (66)	61 (55)	347 (55)
Cardia‡ (percentage of reported cases)	50 (50)	68 (45)	48 (42)	66 (47)	78 (45)	310 (45)
Oesophagus§ (percentage of reported cases)	46 (29)	69 (41)	58 (63)	51 (49)	32 (29)	256 (40)
Cardia§ (percentage of reported cases)	62 (61)	85 (56)	63 (55)	84 (60)	107 (61)	401 (59)
Total	108 (42)	154 (48)	121 (59)	135 (55)	139 (49)	657 (50)

* Classified according to an expanded version of the ICD-7 code[9] inferring that adenocarcinomas of the oesophagus, especially of lower third, were classified as cardia cancers. ICD-0 coding[10] which includes detailed topographic and morphologic information was used from 1978. For the present purpose, ICD-0 code (1978–84) was translated into ICD-7 code. Five patients with tumour of the cervical oesophagus were excluded; † Number of cases per year per 100 000 inhabitants aged 20 years or more of catchment area at midpoint of each 5-year period (Statistical Yearbooks, Danmarks Statistik, Copenhagen 1960–84). The modifications in catchment area and in inclusion and exclusion of reported cases noted above also dictated catchment populations (one for oesophagus, one for cardia, reduction in area from 1970); ‡ See *Figure 1*; § In order to make classification comparable to that of total population adenocarcinomas of lower third of oesophagus (see *Figure 1*) were classified under 'Cardia'. (The data were put at our disposal by courtesy of the Danish Cancer Registry, Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen. The counties of Aarhus, Viborg, Ringkoebing, and North Jutland were considered. Cardia cancers from Ringkoebing County were excluded, since these patients were managed locally throughout the period. Cases from North Jutland County were excluded from 1970 onwards, since the local County Hospital took over treatment in January, 1970.)

varied both with location of the tumour and with the year. Use of the topography given in *Figure 1* for the surgical patients indicated that a higher fraction of oesophageal than cardial tumours underwent operation. This was reversed when the ICD-7 topography used for the background material was also used for the surgical patients (*Table 3*). In both instances, the frequency of surgery during the study remained fairly constant for cardia tumours, while the frequency for oesophageal tumours increased until the mid-1970s whereafter it decreased. *Table 4* shows characteristics of both the background material and of the present surgical cases. The frequency of surgery according to age group was: 59 per cent for patients ⩽49 years ($n=66$); 65 per cent for patients 50–59 years ($n=171$); 68 per cent for patients 60–69 years ($n=355$); 47 per cent for patients 70–79 years ($n=434$); and 20 per cent for patients ⩾80 years ($n=290$; $P<0{\cdot}0001$). The frequency of surgery was 39 per cent for women ($n=434$) and 55 per cent for men ($n=882$; $P<0{\cdot}0001$). Histological diagnoses were available from 1978. When the ICD-7 topography was used for the present surgical material (*Table 4*) the distribution of histological diagnoses in the oesophagus and cardia of background and of surgical cases were comparable. In total, the surgical group included a smaller fraction of squamous cell carcinomas and a higher fraction of adenocarcinomas. During 1978–84 the frequency of surgery was 36 per cent for squamous cell carcinomas ($n=132$) and 56 per cent for adenocarcinomas ($n=258$; $P<0{\cdot}001$).

Discussion

The present surgical patients constitute 94 per cent of all patients referred to the authors' department over 25 years. This was possible because of the aggressive surgical approach, aiming at resection whenever possible, even in disseminated disease. This approach probably also dictated that a relatively high proportion of patients (50 per cent) from our catchment area were operated on and are thus included in the present surgical series. In a recent detailed survey covering more than 6000 cases with oesophageal cancer reported to the Birmingham and West Midlands Cancer Registry, UK, 38 per cent underwent surgery[12]. Depending on whether the topographical classification of the present study (*Figure 1*) or an approximation to the expanded ICD-7 code[9] was used, the frequency of surgery in this study was 55 or 45 per cent for the oesophagus and 40 or 59 per cent for the cardia (*Table 3*). The true figures probably lie in between (i.e. those that would have resulted if it had been possible to use the ICD-0 code[10], which offers detailed topography, on the background material).

The annual incidence of cancers of the cardia in our catchment area showed a steady increase during the study period, which is fully in line with national developments[5]. The declining incidence of oesophageal cancer in the study area also parallels national findings[5]. Given the ICD-7 coding[9] of the background material, inferring especially that lower-third

Table 4 *Sex and age distribution together with histological diagnosis of all reported cases with cancers of the oesophagus and cardia from our catchment area and of the 657 patients with carcinomas who were operated upon (present surgical cases)*

	All reported cases*			Present surgical cases				
	Oesophagus† $n=634$	Cardia† $n=682$	Total $n=1316$	Oesophagus‡ $n=347$	Cardia‡ $n=310$	Oesophagus§ $n=256$	Cardia§ $n=401$	Total $n=657$
Male gender (%)	57 $P<0·0001$	76	67	67 $P<0·0001$	81	62 $P<0·0001$	82	74
Age								
≤19 years (%)	0	0	0	0	0	0	0	0
20–29 years (%)	0	0·2	0·1	0·5	0	0·5	0	0·5
30–39 years (%)	1	1·8	0·9	0·5	2	0·5	2	1·5
40–49 years (%)	3 $P<0·0001$	5	4	4 n.s.	5	4 n.s.	5	4
50–59 years (%)	11	15	13	15	19	15	18	17
60–69 years (%)	26	28	27	38	36	39	37	37
70–79 years (%)	31	34	33	32	30	31	30	31
≥80 years (%)	28	16	22	10	8	10	8	9
Histological diagnosis 1978–84†	$n=126$**	$n=270$††	$n=396$	$n=92$	$n=107$	$n=53$	$n=146$	$n=199$
Squamous cell carcinoma (%)	93·7	5·2	33·3	52	0	91	0	24·1
Adenocarcinoma (%)	5·6	93·0	65·2	45	97·2	4	97·9	72·9
Adenosquamous carcinoma (%)	0·7 $P<0·0001$	0	0·3	0 $P<0·0001$	0	0 $P<0·0001$	0	0
Undifferentiated, small cell, anaplastic carcinoma (%)	0	1·8	1·2	3	2·8	6	2·1	3·0

* See *Table 3*; † see *Table 3*, footnote *; ‡ see *Figure 1*; § see *Table 3*, footnote §, ** eight patients with benign tumours and 22 without histological diagnosis were excluded; †† 16 patients with benign tumours and 18 without histological diagnosis were excluded; n.s., not significant

oesophageal adenocarcinomas were classified as cancers of the cardia, it follows that the annual incidence increase predominantly affects adenocarcinomas of both the lower oesophagus and cardia, while oesophageal squamous cell carcinomas show a declining incidence. Comparable developments for the oesophagus were reported from the Birmingham and West Midlands Cancer Registry[12]; only adenocarcinomas, predominantly those of the lower oesophagus, showed a significant increase in incidence during a 25-year period (1957–81).

Age distribution in the background material and of the patients who were operated on was largely comparable except that a significantly lower fraction of the older patients underwent surgery. Background patients with oesophageal cancer were older than cardia cases, mainly because of a higher fraction of patients in the over 80 age group (*Table 4*). Thus, the age factor probably explained why a lower fraction of patients with squamous cell carcinomas than of those with adenocarcinomas underwent surgery. The more equal distribution between men and women in the former group together with the age factor may explain why the frequency of surgery was lower for women than for men.

The fact that no competitive treatment was available for the patients in this series, together with the above considerations, clearly indicates that patients who did not undergo surgery, contrary to being prognostically better off (in terms of factors such as age and cancer stage), were probably worse off than the surgical patients. With this in mind, it may to some extent be permissible to extrapolate changes noted in this surgical series to the wider population of patients with these cancers

The time-related changes in cancer characteristics noted in the present surgical patients, which paralleled the steady increase in annual incidence of adenocarcinomas of the lower oesophagus and cardia, seem unequivocal. From the first to last 5-year period the fraction of patients having adenocarcinomas increased from a little more than 50 per cent to almost 80 per cent. The most massive change was seen in the case of histological differentiation: the fraction of poorly differentiated carcinomas doubled from one-third in the first 5-year period to two-thirds in the last. The cancers thus showed a clear cut change towards poorly differentiated adenocarcinomas of the lower oesophagus and cardia, the vast majority of which had reached stage III or IV at the time of diagnosis. Similar data have to our knowledge not been published previously.

The distribution of histological types according to location (*Figure 1*) followed the general trend, although the high fraction of adenocarcinomas of the third part of the oesophagus is at variance with most other reports. Adenocarcinomas have been reported to constitute less than 12 per cent of primary oesophageal cancers[12–15], but the mode of classification, of course, may have a massive influence (*Table 4*). A histological re-evaluation of a possible gastric origin of the oesophageal adenocarcinomas in our series, or of origin from columnar lined (Barrett's) oesophagus or oesophageal glands, was not possible given the retrospective nature of our study However, several findings indicated that the high fraction of oesophageal adenocarcinomas here may have some bearing. The 5-year survival rate for adenocarcinomas of the lower third of the oesophagus was no more than 2 per cent (*Table 2*). None of the ten patients with adenocarcinomas of the upper two parts of the oesophagus survived 5 years. These figures should be compared with a 5-year survival rate of 9 per cent for adenocarcinomas of the cardia. Thus, the latter cancers appeared to have a better prognosis than oesophageal adenocarcinomas, despite the fact that degree of histological differentiation, lymph node involvement, stage of the disease and age of the patients did not differ between these three groups. Contrary to what might have been expected from the prognostic differences, a higher fraction of adenocarcinomas of the cardia had extended through the wall (T_3 tumour) and had organ metastases than oesophageal adenocarcinomas. Furthermore, the bulk of the tumour was used to discriminate between the third part of the oesophagus and cardia in cases of extension between the two sites; as the diameters of the cardia tumours were significantly larger than those of oesophageal adenocarcinomas, it follows that the majority of bulky tumours not clearly demarcated in the cardia were actually classified as tumours of the cardia. Tumours of the cardia being larger than the other adenocarcinomas also contrasts with what should have been expected, given the rather strong prognostic influence of tumour size. Cardial and oesophageal adenocarcinomas in the present study thus showed completely different behaviour, indicating that they probably had different aetiological origins, and that the unusually high proportion of tumours in the lower oesophagus is a reliable finding, which all in all puts further stress on the time-related changes previously discussed The present study does not allow comments on possible aetiological factors underlying these changes. In contrast to squamous cell carcinomas, with their well known relation to alcohol intake and tobacco smoking[5], there is no firm knowledge about the aetiology of adenocarcinomas of the oesophagus and cardia[5,13] except for the connection with the relatively rare Barrett's oesophagus[16,17]. Since the Second World War, when the national annual incidence of cancers of the cardia began to rise steadily, the general socioeconomic status of the Danish population has shown a steady rise to a relatively high level. Whether this development has brought about aetiological consequences affecting adenocarcinomas of the oesophagus and cardia is, however, purely speculative.

The grim prognosis of oesophageal adenocarcinomas in the present study is in full accordance with other reports[13,18]. As also noted by Mathiesen *et al.*[1], Earlam and Cunha-Melot[2] and Griffith and Davis[19], but contradicted by others[20,21], it was found here that squamous cell carcinomas had a better prognosis than adenocarcinomas. Location also modified prognosis for the squamous cell carcinomas; long-term survival was somewhat better for the third part of the oesophagus compared with the upper two parts. Almost 50 per cent of the latter patients had T_3 tumour, while organ metastases were more prevalent among those with tumours in the lower third of the oesophagus. Histological differentiation, lymph node involvement and stage did not differ between the squamous cell carcinomas of the two locations. The same tendency for a better prognosis of squamous cell carcinomas of the lower third of the oesophagus relative to the upper two-thirds has been found in several other reports[14,19,22,23]. Akiyama *et al.*[23] noted a higher prevalence of lymph node involvement in tumours of the upper oesophagus, which is at variance with the findings of the present study. Launois *et al.*[24] reported a superior prognosis for middle third squamous cell carcinomas compared with those of the lower third. However, their study differed from the present one in one important aspect: two-thirds of their patients had well differentiated tumours[24].

Patient age and the diameter of the primary tumour mass had a fairly strong prognostic influence, which has also been shown elsewhere[21]. The younger patients, aged 55 years or below, had a slightly poorer prognosis than the following 10-year cohort. Thereafter age showed the usual inverse relationship with survival probability. A tumour diameter of 3 cm or less predicted a 5-year survival rate of 15 per cent. Having exceeded 3 cm, the 5-year survival rate dropped to 8 per cent without substantial influence of a further increase in tumour size. These relationships did not influence the successive worsening of overall prognosis in this study, because patient age and the diameters of primary tumour remained unchanged during the study period.

Stage was a powerful predictor of prognosis in the present study, as is reported by several authors[15,20,25]. Stages III and IV, constituting almost 90 per cent of the surgical patients in 1980–86, had 5-year survival rates of only 5 and 3 per cent, respectively.

The degree of histological differentiation by itself exerted a highly significant impact on prognosis. The 5-year survival rate dropped from 24 per cent for well differentiated cancers to 5 per cent for poorly-differentiated cancers. As the degree of differentiation did not differ between adenocarcinomas and squamous cell carcinomas, or between the different locations, it may be concluded that the increase in poorly-differentiated cancers during the period of the present report was valid, irrespective of histological type and location of the tumour. The pronounced prognostic influence of degree of differentiation excludes the possibility that the changes with time were related to differences in interpretation of the histological sections by different pathologists. Thus, this evolution towards poorly differentiated cancers, together with the resultant increase in the fraction of patients having stage III or IV disease, fully explains why long-term survival worsened progressively during the period of the present study. The 5-year survival rate dropped from 11 per cent for patients operated on during 1960–69 to no more than 3 per cent for those operated on during 1980–84, where almost 90 per cent had stage III or IV disease and two-thirds had a poorly differentiated carcinoma. This worsening of long-term prognosis stands out even more clearly given that the hospital mortality rate actually fell, although statistically insignificantly, from 21 per cent for the 1960s to 15 per cent for the 1980s. This drop in hospital mortality rate should be seen relative to the concomitant increase in the prevalence of patients with stage III–IV disease; these patients had significantly higher hospital mortality rate than those with stage I–II disease.

In another study based on the present surgical material a prognostic index based on T-, N-, and M-classification, together with age and variables underlying general preoperative patient status, such as pre-existing heart and lung diseases, has been developed[4]. This allowed identification of a large group of patients (40 per cent of all patients) where none survived 3 years[4]. As these patients also carried the highest postoperative complication rate, the authors now advocate non-operative palliation in such patients[4]. Given the time-related changes noted in the present report, the fraction of these high-risk patients increased well beyond 50 per cent in 1980–84.

Discouraging as these changes in cancer characteristics are in themselves, they should be looked upon with even greater seriousness given the absence of a therapeutic breakthrough in management of carcinomas of the oesophagus and cardia during the past decades. Recent experience seems to indicate a beneficial influence of combined surgery, chemotherapy, and irradiation on oesophageal squamous cell carcinomas, but only in localized tumours[26]. Therefore, in the present setting, where poorly-differentiated adenocarcinomas in stage III and IV dominate, there seem to be only two alternatives. One is to accept that treatment in the majority of cases can aim only at palliation of dysphagia, which may be performed with a low early mortality rate using endoscopical laser recanalization[27,28] or intubation[29,30]. The other alternative is to diagnose the cancers at earlier stages using such methods as exfoliative cytology during mass screening programmes[31]. Such programmes are, however, not economically practicable in the western world given the relatively low incidence of the disease.

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Protein electrophoresis of diagnostic peritoneal lavage in penetrating abdominal trauma: a marker of significant injury

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Protein electrophoresis of diagnostic peritoneal lavage fluid has been shown in experimental work to be a marker of hollow viscus injury. In order to ascertain the value of this investigation in penetrating abdominal trauma, we conducted a prospective study, over a 4-month period, involving 35 patients with stab wounds to the abdomen whose initial clinical examination was equivocal. The results of electrophoresis were compared with the standard quantitative criteria for diagnostic lavage and the operative findings. Protein electrophoresis was found to be a more sensitive and specific marker of significant intra-abdominal injury than the standard quantitative criteria.

Keywords: Diagnostic peritoneal lavage, protein electrophoresis, penetrating abdominal trauma

Diagnostic peritoneal lavage (DPL) has become the cornerstone of investigation in patients with blunt abdominal trauma in whom clinical assessment is equivocal. Introduced by Root *et al.* in 1965[1] and expanded upon by the same group in 1967[2], it has been shown repeatedly to be a safe and extremely sensitive adjunct to physical examination[3–6]. Numerous attempts have been made to quantify the degree of staining of the lavage effluent and to determine what should constitute a positive return[7–10]. The quantitative standard criteria were introduced nearly 20 years ago[11,12] and, despite minor modifications[13–15], are still in use today (*Table 1*).

Despite obvious success in cases of blunt abdominal trauma, the role of DPL in penetrating trauma remains controversial[16–18]. False negative DPL results as high as 30 per cent have been reported using the standard criteria[19] and suggested red cell counts as indicators for laparotomy vary from 1000 to 100 000 cells/mm^3 (References 20–22). Erroneous results have also been encountered using the standard value for white cell counts[2,23].

The use of protein markers as an aid to the diagnosis of intestinal injury was first suggested from experimental work by Bar-Or in 1983[24]. The purpose of our study was to evaluate the sensitivity of these markers in cases of suspected penetrating abdominal stab wounds and to compare their usefulness with that of the standard criteria for DPL.

Patients and methods

During the 4-month period, from March to June 1988, at the King Edward VIII Hospital, Durban, 121 patients were treated for stab wounds to the abdomen. Following triage, patients were assigned to one of three groups on the basis of physical examination conducted by one of the authors (M.M.). Group 1 ($n = 49$) comprised those patients who required immediate laparotomy (unexplained hypotension, disembowelment, generalized peritonitis, omental protrusion through a chest wound). Group 2 ($n = 37$) comprised patients with no clinical evidence of peritoneal penetration (tenderness confined exclusively to the stab wound, normotension, afebrile). This group underwent repeated clinical assessment. Group 3 comprised those patients with equivocal clinical findings in whom significant injury could neither be confirmed nor excluded on clinical examination alone (tenderness distant from stab wound but without generalized peritonitis, mild pyrexia, normotension). This group of 35 patients underwent preoperative DPL and forms the basis of this study.

There were 32 male patients and three female patients, with an age range of 16–58 years (mean 29 years). Stab wounds involved the flank in seven patients, was between nipple line and costal margin in three, above the umbilicus in 14, below the umbilicus in seven, and involved the back in the remaining four.

DPL was performed using the guidewire method described by Lazarus and Nelson[25] with prepacked sterile kits (American Pharmaseal Company, LNT 9000, Valencia, California, USA). One litre of normal saline was instilled, with a minimum of 50 ml retrieval by gravity necessary to ensure adequate sampling. An adequate quantity was achieved in all cases. Samples of the lavage fluid were then analysed by the haematology laboratory using an automatic Coulter counter (Counter Electronics, Itialeah, France) on unconcentrated lavage fluid. Protein analysis was performed by the biochemistry laboratory using a Beckman Paragon® serum protein electrophoresis kit (Beckman Instruments Inc., Brea, California 92621-6209, USA) after concentration of the lavage fluid in a Minicon-B concentrator (Amicon, Danvers, Massachusetts, USA).

After DPL, all patients were submitted to laparotomy, the surgeon performing the operation being unaware of the lavage results. The operative findings were then compared with lavage values for proteins, white cell count and red cell counts. Strict criteria were used to define positive and negative laparotomies. A positive laparotomy was defined as one in which surgical repair of a damaged viscus was required in order to prevent complications. A negative laparotomy was defined either as one in which there was no peritoneal penetration, or in which, despite penetration, haemoperitoneum, or solid organ injury, no surgical repair was required to effect cure.

Sensitivities, specificities and predictive values were calculated for white cell counts using 500 cells/mm^3 as diagnostic of significant injury, and for various values of red cell counts previously proposed as being diagnostic. Statistical analysis for protein fractions was done using an unpaired Student's t test.

Results

Two patients in group 1 had a negative laparotomy using the aforementioned criteria. One presented with hypotension and

Table 1 *Standard quantitative criteria for diagnostic peritoneal lavage in blunt abdominal trauma*

Aspiration of 5 ml or more of frank blood
White blood cell count > 500 cells/mm^3
Red blood cell count > 100 000 cells/mm^3
Amylase of > 200 units/100 ml
Bile stained effluent
Positive Gram stain
Food particles in effluent
Recovery of lavage fluid via Foley catheter or intercostal drain

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at laparotomy a large laceration which had stopped bleeding was found in the right lobe of the liver. The second patient presented with omental protrusion through a stab wound immediately above the left costal margin. At laparotomy no communication with the pleural cavity could be found, nor was there any intra-abdominal visceral injury. Not one patient in group 2 required operative intervention. In group 3, there were 26 positive laparotomies and nine negative laparotomies (*Table 2*).

Correlation between operative findings and cell counts are shown in *Table 3*, along with sensitivity, specificity and predictive values. Protein fraction measurements for positive and negative laparotomies are shown in *Table 4*.

Cell counts

White blood cells. Although showing a reasonable sensitivity and positive predictive value, the specificity and negative predictive value of the white cell count is poor. The high false negative rate was due, in the main, to four missed pure diaphragmatic injuries, the remaining two missed injuries being a retroperitoneal colonic perforation and a single jejunal perforation. The four false positives were due to moderate haemoperitoneum with no surgically correctable lesion in three patients, and to a completely negative laparotomy with no peritoneal penetration in the remaining patient.

Table 2 *Operative findings in 35 laparotomies*

Positive laparotomy ($n=26$) Organ system injured	n	Negative laparotomy ($n=9$) Findings	n
Small intestine	14	No penetration	4
Stomach	7	Retroperitoneal haematoma	2
Diaphragm	6	Mesenteric laceration	2
Colon	5	Stab wound haemorrhage	1
Liver	5		
Spleen	2		
Pancreas	1		

Red blood cells. From *Table 3*, it can be seen that the use of higher red cell counts decreases the sensitivity and negative predictive value while increasing the positive predictive value and specificity of the test. Use of the standard proposed criterion of 10^5 red cells/mm^3 would have resulted in four missed intestinal perforations (one gastric, one colonic, two jejunal) and four missed diaphragmatic tears out of the six encountered in this series, a false negative rate of 23 per cent overall. Conversely, the use of a low red cell count, 5×10^3/mm^3, would have resulted in an unacceptably high rate of false positives (26 per cent) and subsequent negative laparotomies.

Protein fractions

Comparison of protein fractions in lavage fluids between those patients with injury requiring repair and those without surgically correctable lesions showed statistical significance for all fractions examined (*Table 4*). The α-2 fraction appeared to be the most sensitive indicator of major injury. Overlap between observed ranges in the positive and negative laparotomy groups did not occur in the α-1, α-2, β or γ protein fractions, but was seen on three occasions in the albumin and total protein fractions. The three patients in the positive laparotomy group whose values fell into the observed range in the negative group had all sustained injuries to the diaphragm without other intraperitoneal visceral injury. No significant difference with respect to protein fractions was found between those patients with solid organ injury requiring repair and those with hollow visceral injury.

Discussion

Negative laparotomy for abdominal trauma has a reported mortality rate of up to 6 per cent and a complication rate of between 19 per cent and 23 per cent[26]. As a result, in most centres that manage large numbers of trauma patients, mandatory laparotomy for stab wounds to the abdomen has been superseded by a selective policy[27–31]. Since Shaftan first suggested selective intervention using repeated clinical examination[32], the exploratory laparotomy rate has fallen dramatically[27–34]. Further reduction in the negative laparotomy

Table 3 *Correlation between blood cell counts in diagnostic peritoneal lavage and operative findings*

Cells/mm^3	True positive	True negative	False positive	False negative	Sensitivity (%)	Specificity (%)	Predictive value of a positive test (%)	Predictive value of a negative test (%)
White cells								
500	20	5	4	6	77	56	83	45
Red cells								
5000	26	0	9	0	100	0	74	100
10000	25	3	6	1	96	33	81	75
20000	24	5	4	2	92	56	86	71
100000	18	7	2	8	69	78	90	47

Table 4 *Protein fraction measurements in diagnostic peritoneal lavage in positive and negative laparotomy groups*

	Positive laparotomy		Negative laparotomy		
Protein fraction (g/l)	Range	Mean (s.d.)	Range	Mean (s.d.)	P
α-1	0·035–1·00	0·36 (0·28)	0·015–0·030	0·022 (0·008)	<0·001
α-2	0·25 – 1·75	0·76 (0·48)	0·002–0·04	0·026 (0·012)	<0·001
β	0·20 – 7·50	1·45 (1·71)	0·02 –0·06	0·036 (0·014)	<0·002
γ	0·30 – 4·00	1·62 (1·16)	0·04 –0·08	0·063 (0·015)	<0·001
Albumin	0·18 –10·70	3·80 (2·78)	0·23 –1·60	0·51 (0·41)	<0·001
Total protein	0·26 –18·70	8·02 (5·52)	0·33 –2·90	0·82 (0·79)	<0·001

rate has been achieved by the use of local wound exploration combined with diagnostic peritoneal lavage, should the former prove positive[28,33]. However, no uniform agreement has been reached with regard to standardization of DPL in penetrating trauma and diagnostic cell counts vary considerably from centre to centre[15,19,20–22,28,33,35]. No one set of standard criteria for cell counts can be reliably proposed owing to the wide spectrum of potential injuries. Values that recognize one specific injury, e.g. diaphragmatic penetration[35], are too sensitive for general use, while higher red cell counts will miss significant injuries. Similarly, elevated white cell counts may only arise with peritoneal irritation and injuries producing minimal inflammatory changes in the peritoneum will go unrecognized. Falsely elevated white cell counts may result from autologous blood transfusion into the peritoneal cavity, as witnessed by Root and colleagues[2]. In addition, animal models have shown that leucocyte responses greater than 500 cells/mm^3 can be obtained with minimal peritoneal interference by using unsterile lavage catheters[23].

Previous experimental work showed significant levels of protein fractions, especially the β globulin fraction, in DPL fluid in cases of intestinal injury[24]. Our own clinical study has found that in penetrating trauma, there is a highly significant difference in all protein fractions between those patients who require surgical intervention and those with either minor injuries or no peritoneal penetration.

Electrophoresis of lavage fluid requires 40–60 min to perform. For this reason, clinical examination should remain the mainstay of assessment in cases of penetrating torso trauma. Those patients who exhibit obvious signs of intraperitoneal injury should be submitted to laparotomy without further specialized investigation. Likewise, those patients whose initial clinical assessment shows no evidence of peritoneal penetration may safely undergo repeated examination on a 2-hourly basis[30]. Although the numbers in this study are small, statistical analysis indicates that protein electrophoresis of DPL in patients with equivocal clinical findings may help identify those who require surgical intervention for their injuries. Electrophoresis of the lavage effluent in this group of patients could, by the time repeat clinical examination was appropriate, indicate whether surgical intervention is required or not, thus avoiding both unnecessary delay and negative laparotomies.

Protein electrophoresis relies neither on peritoneal contamination nor extravasation of red blood cells and appears to be a more sensitive and specific investigation than cell counting. Its use in the future, if specific ranges for significant and insignificant injury can be reliably documented, may reduce the number of unnecessary operations and prevent avoidable delay with its ensuing complications in those who require surgery for their injuries.

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Presentation of manuscripts for publication in The British Journal of Surgery

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> You don't write because you want to say something; you write because you've got something to say.
>
> F. Scott Fitzgerald

Most surgeons are impatient perfectionists. They have little time to spare for reading outside their subjects, and what reading they do is probably done while travelling, between operations, or late at night. It is perhaps not surprising, therefore, that they are prepared to tolerate – both in their reading and their writing – convoluted prose, sloppy analyses, careless presentations, and unfounded conclusions. A proportion of the manuscripts submitted for publication in *The British Journal of Surgery* during the past few months contained one or more of these defects.

Some of the examples were minor – for example, miscalculation of percentages, spelling mistakes and the use of unexplained abbreviations. Some, however, were more serious and could have undermined the editors' determination to maintain the highest standards of ethical and scientific integrity and surgical reliability. Some authors did not supply enough information for readers to place any reliance on either their results or their conclusions; some quoted percentages inappropriately, given the smallness of their samples, and some did not differentiate between statistical significance and biological relevance, coming to conclusions that were potentially misleading

This article is not a criticism of the editors. Their principal tasks are to publish ideas, techniques and trials that are interesting and may have a potential for altering clinical practice, as well as controversial statements and authoritative reviews. As most surgeons are not trained in techniques of presentation it does mean that both scientific and technical editors have to spend a lot of time trying to eliminate errors before the papers are printed; their burden would be lighter if authors took the trouble to submit manuscripts that were free from at least the most obvious solecisms.

In this paper I illustrate some of these points, and suggest remedies for the grossest errors of presentation. I must emphasize that many of the defects were corrected before the papers were published and that my analysis was of the manuscripts.

Major faults in presentation

Ethics

Most authors reporting controlled trials were careful to point out that either the trial had been approved by their local ethics committee, or the patients had given *informed* (my italics) consent; the extent of information given, and particularly the way in which the process of randomization was explained to patients, however, was usually not mentioned. This is not of particular moment if the experimental procedure being studied is of no pressing concern to the patient, but it is a matter which must be considered.

Inadequate definitions

Several studies, which had the potential for altering clinical practice, were rendered less effective than they might have been because they either omitted, or gave inadequate, definitions of events, methods or end points. Such definitions are particularly important in multicentre studies. For example, Cahill *et al.*[2] reported a study of sutureless colonic anastomosis using a biofragmentable ring. This was carried out in six countries and the authors stated that 'Anastomotic leakage, wound infection and subacute obstruction rates reported are those detected clinically' That is all For all the reader knows one hospital could have defined wound infection as redness around the wound, while another accepted only total breakdown.

Clason *et al.*[3] argued in favour of the centralization of vascular surgery to units with a vascular interest, by comparing morbidity and mortality during two periods of time for patients with acute ischaemia of the lower limb. They did not, however, give full details about the comparability of the two groups for some of the risk factors known to have adverse effects on such patients It is possible that the improvement in morbidity between the two periods could have been caused by an imbalance of the proportions of smokers, or diabetics, or older patients, in one of the groups.

Sarin and Lightwood[4] reported an audit or 66 upper and 65 lower gastrointestinal anastomoses constructed with a continuous single layer polyglycolic acid suture Their complication rates were acceptable, but they failed to define what they meant by wound infection and anastomotic breakdown. Readers might also have appreciated reference to earlier experimental studies of healing after single layer continuous suturing of the colon[5].

It is a habit among authors who have made a study of a subject to assume that everybody else knows as much about it as they do. Indeed that probably applies also to the referees of papers, as they have been chosen by the editors because of their special interest. It would have helped general readers, however, to understand the paper by Fisher *et al.*[6], had they been told what the 'functional score' was, and the paper by Ashley *et al.*[7] would have been clearer if 'Bloom's grade' had been explained.

Retrospective studies are useful, particularly when rare diseases or uncommon operations are reported. They are marred, however, if the method of acquiring the data is not mentioned. It is a brave man who states that he studied *all* patients with a particular condition[8,9]; data collected for administrative purposes are well known to be inadequate and inaccurate[10], and audits based on these data are seldom complete[11].

Type III errors

Type III errors were first described by Condon[12] who defined them as ways in which 'the conclusions drawn are not supported by the data presented' Murray *et al.*[13] implied in the first sentence of their Discussion that their technique of ultrasonic

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shock wave disintegration of gall stones was clinically useful; what they had actually shown was that they had fragmented 55 stones in the laboratory at wave lengths that had been shown to be safe (in rats).

Taylor and Morris[14] committed a Type II and a Type III error when they referred to a trend ('Praziquantel alone showed a trend to being more effective [in gerbils] than albendazole at reducing the number of [hydatid] cysts'). What they really meant was that they had not studied enough gerbils to prove or disprove the null hypothesis, and they failed to emphasize that gerbils may react differently from people.

Several authors equated statistical significance with clinical relevance or biological importance. Some journals now require that confidence intervals are stated instead of (or as well as) P values to minimize this error, but the idea that '$P<0{\cdot}05$ = the truth' is firmly ingrained. For example, Fisher *et al.*[6] claimed that 13 constipated patients who were improved by operation (we are not told what operation) had lower preoperative anxiety scores and lower depression scores than eight similar patients who were not improved. Despite achieving statistical significance ($P<0{\cdot}05$ and $P<0{\cdot}02$, respectively) the overlaps between the groups (scores 3 to 14 compared with 10 to 19, and 2 to 12 compared with 5 to 11) were such that it is obvious that there were no determinant differences between the groups for either score. There is also a move by some statistical advisers to ban the use of the abbreviation 'NS' on the grounds that the idea that 'NS = not significant' therefore 'not so' is as bad as '$P<0{\cdot}05$ = the truth'.

Leahy[15] deserves credit for putting forward a new technique (laparoscopic appendicectomy) that can reduce the length of time spent in hospital after operation. We are told that the patients were generally fit to leave hospital the day after operation, and that they returned to work or normal activities within a week. All well and good had he left it there, but in his Discussion he stated that: 'The absence of postoperative adhesions is important especially in female patients.' This is a far reaching conclusion on the experience of four patients, neither the sex nor the length of follow-up of whom are mentioned. Adhesions are less formidable after laparoscopic sterilization than after laparotomy, but it is by no means certain that this will also be the case after appendicectomy.

Moving up the gastrointestinal tract, and also into the fashionable area of allotting 'scores' to patients' degrees of risk, Schein and Gecelter[16] maintained that it is possible to use the APACHE II score to stratify patients with upper gastrointestinal bleeding on admission to hospital into high and low risk groups so that the best treatment can be chosen for each patient. Their survey was carried out retrospectively (though we are told the method by which the information was garnered) and the conclusions were not validated prospectively in a comparable group of patients. How many methods and ideas that seemed proved by a retrospective survey have bitten the dust when subjected to the objectivity of a prospective validation? Not only that, but Knaus himself would be the first to admit that APACHE II was not designed to stratify individual patients before operation; it was designed to allow comparison of the results of treatment within single intensive care units, or among those in different hospitals. In addition, I suspect that there are few hospitals in which a surgeon can rely on getting a comparatively complicated form filled in (including results of measurements of white cell count and serum concentrations of haemoglobin, creatinine, sodium, and potassium, as well as blood gas analyses) in 'under half an hour'.

I have already mentioned the multicentre trial by Cahill *et al.*[2] (of three methods of large bowel anastomosis) as being flawed by its lack of definitions. Among their conclusions was that: 'Adequacy of bowel preparation was reported as excellent or good in 84 per cent of cases, and as poor in only 3 per cent, with no difference between the groups.' To illustrate this they showed a table (*Table 4*) in which the numbers of patients receiving each type of bowel preparation (mechanical [unexplained], laxative, and enema) are given, as are the numbers receiving antibiotics [unspecified] and the route of administration (systemic or oral). What is not stated is how many patients received any particular combination or combinations of bowel preparation. It is possible from the table to deduce that 11 of 101 patients (10·9 per cent), six of 16 patients (38 per cent) and five of 85 patients (6 per cent) in the three groups, respectively, did not receive any antibiotics at all. It is, therefore, possible that the degree of bacterial contamination differed significantly among the groups, bringing into question an important aspect of their comparability that is not covered by *Table 1* (Patient details), but which could have had a profound influence on the results of the trial.

Again concerning operations on the large bowel, Horgan *et al.*[17] concluded that anal sphincter pressures were reduced after low anterior resection and that this reduction was caused by direct injury to the internal sphincter. In *Table 1* they give the preoperative measurement – we are not told if it is mean (standard deviation) or mean (standard error) – as 67(4), the measurement 10 days after operation as 51(4), and the measurement 6 months later as 53(5). In *Table 2*, however, the preanaesthetic value is given as 55(6); it is only in the text that it is disclosed that this value was obtained after premedication with a benzodiazepine. It does not differ significantly from the value 6 months after operation.

The last example of a Type III error is from Bird *et al.*[18] who suggested that: '...measurement of serum phospholipase A_2 activity may provide a simple test for the early identification of most patients with severe acute pancreatitis.' It may well do so, but the argument would have been more convincing had they compared the prognostic value of the test with the clinical outcome rather than with the results of another predictive test (Ranson) which, though it may be the best we have, is recognized as being less than perfect.

Inappropriate manipulation of numbers

I shall restrict myself to noting some of the more obvious statistical errors, as the topic has been reviewed by Murray[19] and I commend his paper. One of the most common ways in which authors manipulated numbers inappropriately was by using percentages in reporting their results. For example, Ball *et al.*[11] stated that: '88 per cent of patients over 70 who died had a preoperative blood urea above 15 mmol/l'. This sounds an enormous number, but study of the tables and methods shows that it means seven out of eight patients. Levy *et al.*[20] do give total numbers for their main groups, but give only percentages for morbidity and mortality within subgroups so that it is impossible to tell how many patients they are writing about in particular parts of the paper.

To take the use of percentages to its most ridiculous extreme, Kern *et al.*[21] referred to 3·5 per cent of 46 patients – this is 1·6 patients. Taberner *et al.*[22] wrote that of 14 patients in one group, 7·1 per cent were male, when what they meant was that there was one man. It is a convention of scientific writing that percentages should not be used at all if the total number is less than 25, they should be given in whole numbers if the total number is between 25 and 100, and only if the total number is greater than 100, may figures be given to one decimal place – and only one.

Percentages have their place, which is to compare one series with another. I fail to see the point of hiding raw data behind percentages, though authors may feel that publication of these calculations is expected of them. The author has to have the raw data to calculate them in the first place so he is making extra work for himself; this leads to the inevitable and sometimes correct conclusion that he is trying to conceal the small size of his sample. Canivet *et al.*[8] also used misleading percentages, it was not apparent until the data were 'tortured until they confessed'[23], that the percentage referred to a different number out of a different total on nearly every occasion.

Another common manipulation of numbers was the use of means and standard deviations (or standard errors) instead of medians and ranges (or interquartiles) for data that were not normally distributed. Murray[19] has already pointed this out, but his advice seems to have been unheeded. The standard deviation is a measure of the scatter of observations around the mean. If data are normally distributed, 95 per cent of the observations will lie within two standard deviations on either side of the mean; if the standard deviation is more than half the mean, therefore, the data are unlikely to be normally distributed. One example of the misuse of means and standard deviations is in the reporting of the length of hospital stay (which is never normally distributed); in several reports the figures seem to show that some patients left hospital before they were admitted.

Stansby and Greatorex[24] were clearly dealing with skewed distributions when they give the mean (s.d.) time to healing (in weeks) of pilonidal sinuses treated by excision and packing as 13·0 (7·5), range 2 to 37, compared with the time after phenol injection: 8·7 (5·5), range 1 to 23. They then report – despite such an enormous overlap – that this difference is highly significant ($P<0·001$) using Student's t test. One of the paradoxically reassuring things about this is that if they had not reported the range the overlap would not have been nearly so obvious.

There seems to be a widely held belief that a paper without P values is unpublishable. It is, however, obvious that some authors are ignorant of the purpose of tests of probability. For example, Pimpl *et al.*[25] felt it necessary to point out that 1 out of 100 was not significantly different from 0 out of 181, and disclosed that $P>0·1$.

All active drugs have unwanted side effects and the same may be said of computers. One of these is that they allow easy access to statistical tests that seem to give credence to even the most inadequate data. Fisher *et al.*[6] did a multivariate analysis of 11 variables in 65 patients, and Civalleri *et al.*[26] divided 35 patients first into three subgroups, and then each into a further five subgroups; they then applied statistical tests to the differences, and found that some of them were significant.

I am not sure that one should go as far as one eminent statistician and say that if a study needs sophisticated statistical analysis to prove a point it probably does not have much biological (or clinical) relevance, but I do urge that readers should use their common sense: *caveat emptor*.

Minor faults in presentation

Most of the minor faults in presentation can be attributed to carelessness. The prolific use of abbreviations, usually unnecessary, is not only thoughtless but bad manners. Many readers of *The British Journal of Surgery* have languages other than English as their mother tongues, and abbreviations confuse rather than help them. For example, CNS to one person means central nervous system, to another, coagulase negative staphylococcus. I came across the abbreviation CT used to mean 'cytotoxic chemotherapy' in a paper I was editing for another journal. Common sense tells us that long phrases like enzyme-linked immunosorbent assay (ELISA) may be abbreviated, but should always be spelled out the first time they are used. To abbreviate a term that is used only once or twice is unnecessary: fine needle aspiration biopsy was abbreviated to FNAB by Mitchell *et al.* in their Introduction, but mentioned only once more[27]. I await with interest the spelled out versions of M-AMSA[28] and FUdr[26].

Carelessness of expression may cause the reader to be confused about numbers in groups. Michaels *et al.*[29] studied: 'a total of 40 laser procedures … on 37 legs of 34 patients'. They reported that 13 procedures failed to recanalize the superficial femoral arteries; further on in the same paragraph, however, the number of failures was $5+2+3+4+2+2=18$. Authors should take great care to distinguish among totals, and make it absolutely clear to which they refer.

Naylor *et al.*[30] reported the causes of graft occlusion after aortofemoral bypass for peripheral ischaemia, and offended me by giving their results almost entirely in percentages. They also gave numbers in such a way that they could have referred either to subgroups of the total, or to separate groups in addition to the total. Presentation of the data in tables rather than in the text would have made them easier to follow.

Tables and figures

Every table and figure must have a title that requires no reference to the text for the reader to understand what it illustrates. If a table or a figure contains a lot of information a key may have to be included in a *brief* footnote, but long explanations should appear in the text. Better two simple tables than one complex one. Methods of interpreting scans, for example, should be described in the Patients and methods section, not in the figure legend[26].

Mistakes in diagrams included: the bars representing standard deviations above and below the mean were different lengths[31], the number of dots on a scattergram did not correspond to the number of patients given in the text[6], and the increments on the vertical axis of a graph differed by as much as 1 mm[29]. These mistakes show that the work was not checked adequately when it was returned from the medical art department.

Histograms were used quite often, and while they do have a place (when only an impression of the differences among proportions is important), in many cases, for example Winkler *et al.*[32], tabulation of the data would have been more informative as well as being easier to understand.

Matters of style

Most of the papers accepted by the journal were well written and contained none of the errors I have mentioned. I shall say little about the grammatical mistakes, convoluted sentences and tortuous prose found in a minority of papers. The first are usually corrected by the sub-editors and, concerning the last two, the extent to which style should be imposed by editors is a matter of opinion. Language should be '… a precision tool, conforming to simple rules and conveying meaning logically'[33].

On balance I come down in favour of the imposition of a fairly rigid style, principally because the aim of writing is not only to make yourself understood, but also to make certain that you are not misunderstood[34]. *The British Journal of Surgery* favours a more liberal approach to stylistic matters; nevertheless, nouns should not be used as verbs, verbs as nouns, or adjectives as adverbs. Superfluous words should be cut out. Purists may well be offended by such examples as Karanjia and Giddings[35] 'Histology of the biopsies' ('histological examination of biopsy specimens') and Mitchell *et al* [27] 'pancreatic mass lesion' ('pancreatic mass'). I sympathize with the 23 patients mentioned by Wilson *et al.*[36] who 'will soon achieve obliteration'.

I was pleased to see that only one abstract stated that 'The implications .. are discussed'[37]. Abstracts on the whole were informative, but there were still a few that were written in the active voice: abstracts should always be in the passive voice because they are often printed without alteration in abstracting journals. Several papers used the words 'approximate' and 'average' – surely too vague for serious scientific communications – and there was commonly confusion between 'prevalence' and 'incidence'. In a few papers there was a lack of consistency in terminology; to criticize this might be considered nit picking when the terms used were practically synonymous (for example, stricture and stenosis[6]), but carelessness in small matters undermines one's confidence in the authors' ability to deal correctly with large ones. Archy the cockroach could have been describing the philosophy of some medical writers when he wrote[38]: '*i never think at all when i write/nobody can do two things at the same time/and do them well*'.

This is a personal view, and I have no doubt that many will disagree with me. I do feel, however, that good research deserves to be presented well and that good presentation is as much a part of the research as the collection and analysis of the data. I have the impression that too many people submit manuscripts that have not been sufficiently edited, particularly by their senior authors whose help in the final stages of preparation of a manuscript may be perfunctory. This not only detracts from (and sometimes conceals) a valid message, but also reflects no credit on the writers or their critical faculties. We recognize good writing when we see it; let us also recognize that science has the right to be written well.

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Case report

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Intraoperative internal carotid artery restenosis detected by transcranial Doppler monitoring

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Several reports have described the monitoring of blood flow in the middle cerebral artery during carotid endarterectomy by means of transcranial Doppler sonography$^{1-5}$. The clinical applications of this method have still to be established$^{1-5}$. The value of monitoring by transcranial Doppler sonography is demonstrated in a patient who developed signs of restenosis during surgery.

Case report

A 65-year-old man presented with right-sided amaurosis fugax. Duplex Doppler ultrasound and transfemoral angiography demonstrated an occluded internal carotid artery on the left and 80–99 per cent stenosis on the right. Preoperative transcranial Doppler sonography (EME TC2-64 B®, EME GmbH Ueberlingen, FRG) findings are shown in *Table 1*. A right carotid endarterectomy with a venous patch was performed. By means of a fixed flat probe on the right temple, permitting a constant insonation angle, continuous transcranial Doppler sonographic monitoring of the right middle cerebral artery (*Figure 1*) mirrored the events described by Padayachee *et al.*[1]. Preclamp values at a depth of 50 mm were: mean blood flow velocity (MBFV) 52 cm/s, pulsatility index (PI) 0·53. Clamping of the right carotid artery caused an immediate drop in the MBFV in the right middle cerebral artery to 20–22 cm/s, indicating a residual flow of approximately 38 per cent PI was reduced to 0·28 (53 per cent of the preclamping value) A shunt was used because of low stump pressure (10–11 mmHg). The shunt caused an increase in the MBFV of the right middle cerebral artery to 32 cm/s (61 per cent of preclamping MBFV) and PI rose to 0·44 (83 per cent of the preclamping value). Immediately after endarterectomy and removal of the clamp, MBFV increased to 56–60 cm/s and PI to 0·72–0·76 (a 36 per cent increase compared with the preclamping value)

During wound closure these values remained unchanged. Gradual declines in both MBFV and PI were noted after 3 min while the patient was still under general anaesthesia with unchanged and stable blood pressure (80–90/40–50 mmHg, measured intra-arterially) The MBFV of the right middle cerebral artery shifted from 60 to 22 cm/s, and PI was lowered from 0·76 to 0·25, indicating a situation equivalent to the clamping procedure. A restenosis was suspected.

A second look at the operating site revealed no abnormalities. Good pulsations were felt in the entire length of the exposed internal carotid artery. Thereafter the flow pattern of the right middle cerebral artery showed some oscillations of MBFV and PI, ranging between clamping and shunt values and suggesting a restenosis of fluctuating severity. Intra-arterial mean blood pressure measurements across the operating site showed no changes. A peroperative carotid angiogram showed poor filling of both the external and internal carotid arteries, indicating obstruction at the site of surgery.

The bifurcation was re-explored. Clamping and shunt procedures caused the same transcranial Doppler sonography patterns as before (*Figure 1*). Inspection of the reopened carotid artery showed a dorsally situated intimal flap at the distal end of the arteriotomy. This was sutured and a new venous patch was implanted.

After release of the clamp, MBFV in the right middle cerebral artery was 76 cm/s and PI was 1·00. Postoperative measurements showed the same values, and the patient regained consciousness without neurological sequelae. The following day transcranial Doppler

Table 1 *Preoperative and postoperative transcranial Doppler sonography*

	Right			Left		
		After operation			After operation	
	Before operation	Day 1	Day 40	Before operation	Day 1	Day 40
Ophthalmic artery (50-mm depth)						
SBFV	82	82	60	160*	140*	68*
MBFV	54	42	24	80	80	34
PI	1·13	1·32	3·58	1·03	1·03	1·32
Middle cerebral artery (50-mm depth)						
SBFV	90	132	112	62	86	102
MBFV	62	72	70	44	50	64
PI	0·68	1·23	0·99	0·60	0·87	0·82
Anterior cerebral artery (65-mm depth)						
SBFV	140	158	164	*	*	*
MBFV	96	96	136			
PI	0·72	1·01	0·69			
Posterior cerebral artery (65-mm depth)						
SBFV	100	112	76	100	56	92
MBFV	58	56	44	56	32	46
PI	0·99	1·15	0·98	1·01	1·26	1·04
PTI (middle cerebral artery, reference: basilar artery)	0·77	1·05	0·95	0·68	0·74	0·79
Basilar artery (85-mm depth)						
SBFV	98	74	80			
MBFV	62	42	46			
PI	0·88	1·17	1·04			

* Reversed flow direction; SBFV, systolic blood flow velocity (cm/s), MBFV, mean blood flow velocity (cm/s); PI, pulsatility index; PTI, pulsatility transmission index

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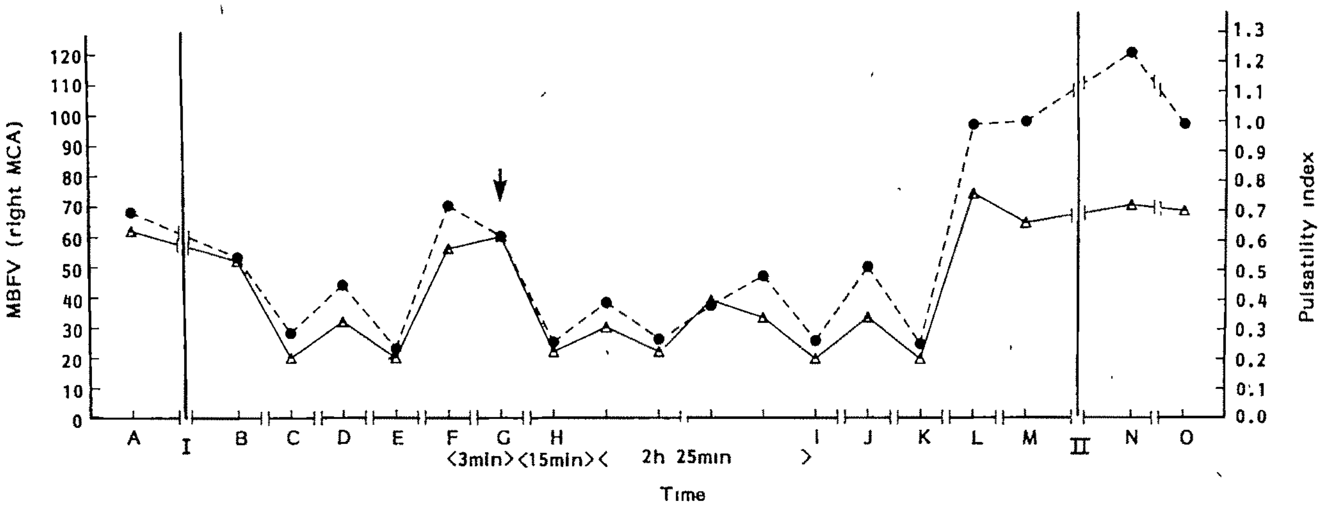

Figure 1 *Transcranial Doppler sonography. preoperative, intraoperative and postoperative parameters from the right middle cerebral artery (MCA), depth setting 50 mm.* △, *Representative values of the mean blood flow velocity (MBFV),* ●, *representative values of the pulsatility index Related events are shown on the x axis as follows: A, preoperative values,* I–II, *right carotid endarterectomy (continuous monitoring B–L), B, under anaesthesia, C and E, clamp* I *on, D, shunt* I, *F, clamp* I *off, G, start gradual decline (arrow), H, situation equivalent to clamp procedure; H–I, oscillations, I and K, clamp* II *on; J, shunt* II; *L, clamp* II *off; M, recovery room; N, day 1 after operation; O: day 40 after operation. Time intervals are shown between brackets*

sonography showed a normal flow pattern in the right middle cerebral artery with a pulsatility transmission index (PTI) of 1·05 (reference· basilar artery, normal >0.92) (Reference 6), indicating a restored and unimpeded flow in the right internal carotid artery (see *Table 1*).

Forty days after carotid endarterectomy transcranial Doppler sonography recording was unchanged (*Figure 1, Table 1*) with a normal PTI (0.95) of the right middle cerebral artery (reference. basilar artery). Duplex scanning of the right bifurcation showed no signs of restenosis.

Discussion

Non-invasive basal cerebral artery blood flow velocity measurement by transcranial Doppler sonography has been available since 1982[7]. This type of monitoring in carotid endarterectomy has been used to decide whether to apply a shunt or not[4], a procedure known to have certain hazards[8]. The number of early restenoses after carotid endarterectomy is unknown[9]. The restenosis in our patient caused oscillating changes in MBFV and PI of the ipsilateral middle cerebral artery compatible with a fluctuating haemodynamically significant lesion, presumably due to an intimal flap. Early intraoperative restenosis of the carotid artery detected by transcranial Doppler sonography monitoring of the middle cerebral artery during endarterectomy has not been reported before This type of monitoring may prove to be useful when intraoperative angiography or duplex scanning are not available routinely.

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Congenital diaphragmatic hernia

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Congenital diaphragmatic hernia most commonly presents as an acute neonatal surgical emergency on the first day of life and has a mortality rate approaching 50 per cent[1]. Babies who present after the first 24 h of life have a much better prognosis. In the majority of cases the diagnosis is suspected on clinical grounds and is confirmed by the classical radiological features[2]. Our patient presented with an unusual history, and although the correct diagnosis was suspected on the first chest radiograph, subsequent films, with complete disappearance of the herniated gut, led to a delay in confirmation of the diagnosis.

Case report

A male infant was born by normal delivery on 24 June 1988, at 36 weeks' gestation. Apgar scores were 8 and 10 at 1 and 5 min respectively. He had transient tachypnoea of the newborn but made a smooth recovery and went home 96 h later. He re-presented on 3 and 11 August 1988 with a history of constipation and bleeding *per rectum*. An anal fissure was diagnosed and treated conservatively. He presented again on 14 August with acute respiratory failure. Before admission he had been straining to pass stool, became red and was shaking, then went blue and flaccid for 1 min. On arrival at hospital he was still cyanosed and irritable, with tachypnoea and tachycardia. His abdomen was tender in the right hypochondrium, and on chest examination there were bilateral crepitations. Laboratory investigations showed a mild metabolic acidosis and a haemoglobin of 8 g/dl. He was resuscitated with blood and plasma infusion. A chest radiograph (*Figure 1*) showed almost complete opacity of the left hemithorax, right upper lobe pneumonia, and mediastinal shift to the right. A provisional diagnosis of left congenital diaphragmatic hernia was made, an endotracheal tube was passed, and the patient was referred to the Children's Hospital in Sheffield.

On arrival, repeat chest radiograph revealed that the endotracheal tube had slipped into the right main bronchus (*Figure 2*). Following neuromuscular blockade and reintubation, a chest radiograph showed complete aeration of the left lung (*Figure 3*) and the patient made a dramatic improvement, but the apex beat did not return to a normal position. He was ventilated electively from 14 until 18 August, and then extubated. He remained well until 18 h later when he became tachypnoeic and the transcutaneous P_{O_2} dropped from 14 kPa to 8 kPa. A repeat chest radiograph showed the classical features of a left congenital diaphragmatic hernia (*Figure 4*).

At laparotomy the intestine was found to be normally rotated and in the abdominal cavity. There was a small left posterolateral diaphragmatic defect 5 cm in diameter with the spleen trapped in the pleural cavity. We had to extend the defect to deliver the spleen into the abdomen before repair. The baby made an excellent postoperative recovery.

Discussion

This infant presented an unusual and interesting picture with potentially serious consequences. The referring paediatrician established the correct diagnosis. Confusion arose from the initial radiograph taken after transfer showing the misplaced endotracheal tube and complete absence of gas in the left hemithorax. The immediate clinical and radiological improvement following reintubation led us to conclude that there had been solely an obstructive airway problem. Insufficient attention was paid to the evidence of persisting mediastinal shift, and the possibility of a diaphragmatic hernia was dismissed.

We consider that the spleen acted as a plug in the diaphragmatic defect, a situation previously reported by Rø et al.[3]. While there was a small differential pressure between abdomen and chest, no herniation of gut could occur. However, the straining due to constipation may easily have so increased the intra-abdominal pressure that the spleen was displaced and herniation of gut occurred. When neuromuscular paralysis and full ventilation were established, the positive intrathoracic pressure forced the gut back into the abdomen, only to reherniate after extubation. We suggest that the gut was not forced back into the abdomen at the initial phase of ventilation because at that time the spleen blocked the defect in the opposite direction to its previous plugging effect. This unusual clinical picture has not been previously described.

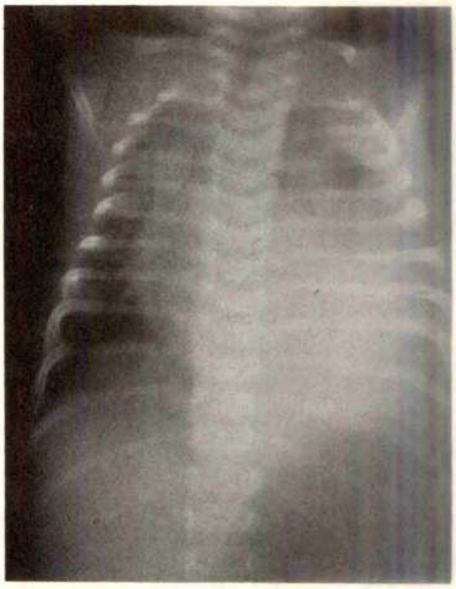

Figure 1 *Chest radiograph taken after initial resuscitation*

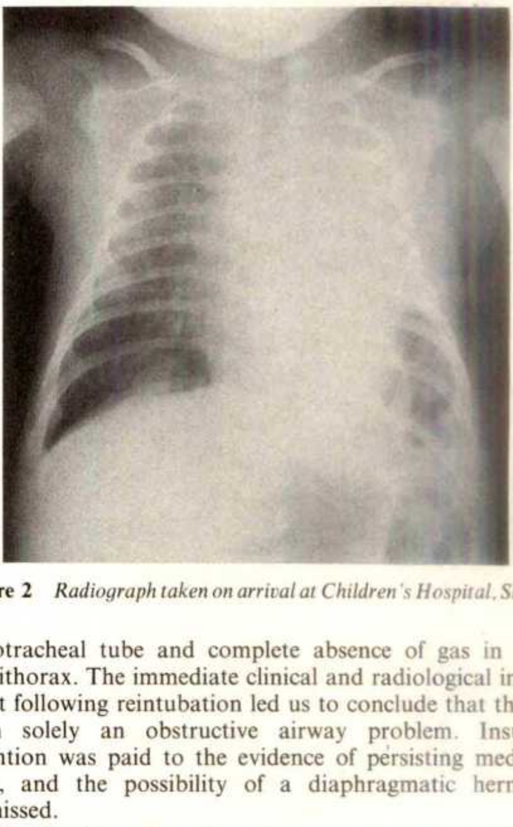

Figure 2 *Radiograph taken on arrival at Children's Hospital, Sheffield*

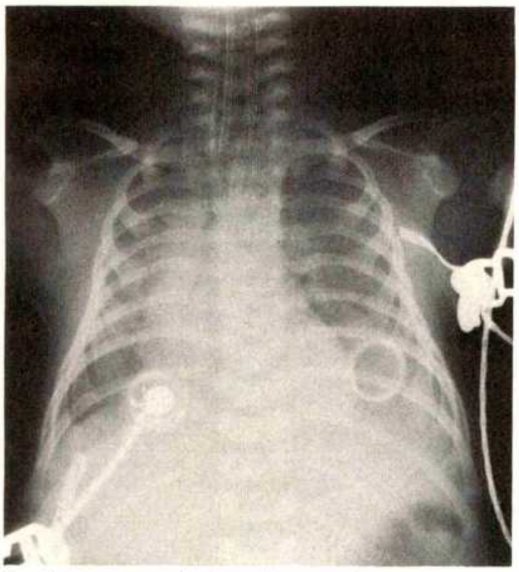

Figure 3 *Chest radiograph taken after reintubation*

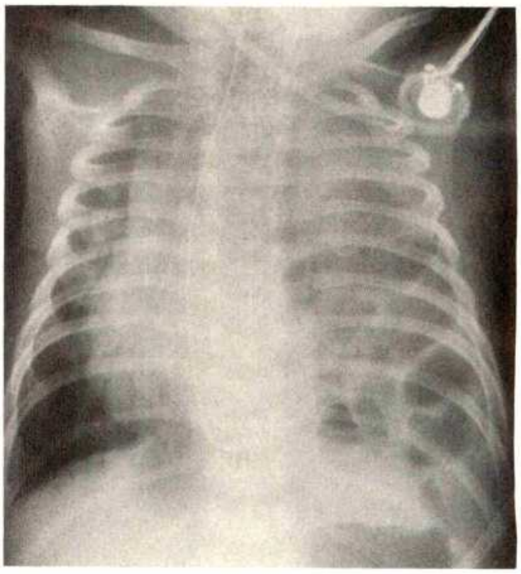

Figure 4 *Chest radiograph taken before repair of hernia*

Acknowledgement

We are grateful to Mrs A. Jones for typing the manuscript.

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Short note

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^{99m}Tc-labelled HIDA scintigraphy in assessment of bile leakage after removal of T tube from the common bile duct

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Bile peritonitis occurring after removal of a T tube from the common bile duct is generally regarded as a rare, but potentially fatal, complication[1,2]. This study investigates whether the information obtained by scintigraphy with ^{99m}Tc-labelled Sn-2,6-di-ethylacetanilidoiminodiacetic (^{99m}Tc-labelled HIDA) can contribute to the selection of patients requiring reoperation because of bile peritonitis.

Patients and methods

Ten patients, six women and four men with gallstone disease, median age 69 years, all of whom had a normal hepatic function and normal T tube cholangiography, had scintigraphy 24 h after T tube removal, as previously reported[3,4]. Recording of polaroid pictures from an oscilloscope was performed and each image covered 4 min.

Results

The T tubes were removed after a median of 8 days (range 8–10 days).

The patients fell into three groups. The first group comprised six patients who demonstrated normal findings: all had an uneventful course. In the second group of two patients nearly all the activity was in the duodenum. In one patient who had no symptoms, some activity was present in the gallbladder bed. The second patient demonstrated a more widespread accumulation of activity in the subhepatic area and he had clinical signs of bile periotonitis; he was treated conservatively. This patient was discharged, but readmitted 13 days after removal of the T tube to be treated surgically for a symptomatic subhepatic accumulation of bile. In the third group (two patients), all the activity extravasated into the peritoneal cavity (*Figure 1*). Both patients developed bile peritonitis requiring reoperation and reinsertion of a T tube. These operations were performed 29 h and 79 h after removal of the T tube.

Discussion

After T tube removal from the common bile duct, where symptoms suggestive of a major bile leak arise, diagnosis by X-ray examination is uninformative[5]. Ultrasonography and computed tomography are clinically accurate techniques. However, these techniques are unable to determine if a fluid collection is due to bile or blood or if bile is passing into the duodenum.

Based on the reservations mentioned above we evaluated ^{99m}Tc-labelled HIDA scintigraphy. In normals this examination clearly delineates the liver and the extrahepatic biliary tract. Activity in the duodenum is usually seen within 1 h and earlier in a subject with a normal hepatic function and a previous cholecystectomy[6]. Activity outside the liver, biliary tract, and intestine is easily identified. The findings in this study demonstrate that there is a relationship between the scintigraphic findings and the clinical course. As expected, the most common finding was activity within the biliary tract and duodenum and all these patients had a normal clinical course. Among the two patients with subhepatic accumulation of activity as well as intestinal activity, the one with the most pronounced leakage was readmitted and treated for a subhepatic accumulation of bile. The two patients who had no intestinal activity both developed clinical signs of peritonitis and were operated on. Scintigraphy was performed 24 h after removal of the T tube in this study, but it is probable that the same information can be obtained if the investigation is performed a few hours after removal of the T tube. If the pain after a T tube removal persists we recommend that ^{99m}Tc-labelled HIDA scintigraphy is performed. Immediate surgery is advocated when no activity passes to the duodenum. If the scintigraphy demonstrates activity in the intestine as well as extravasation of activity into the peritoneal cavity then the patient should be monitored closely and the indication for surgery based on the subsequent clinical course.

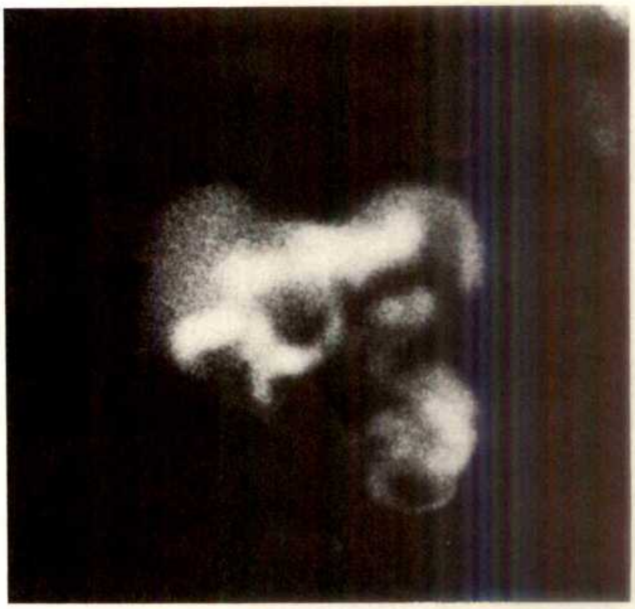

Figure 1 *^{99m}Tc-labelled HIDA scintigraphy demonstrating extravasation of all activity to the peritoneal cavity*

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Salvage of an exposed arterial prosthesis by tissue expansion

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Tissue expansion is well established in reconstructive procedures. The first case of controlled tissue expansion was performed by Neuman in 1957[1] by means of an inflatable device placed subcutaneously in the reconstruction of an ear. This technique has since been popularized in breast reconstruction[2–4], in the head and neck region[5] and in the upper and lower extremities. However, the principle is not widely applied in the general surgical field. We report a case in which a groin defect with an exposed arterial prosthesis was covered with the help of tissue expansion when none of the normally available local flaps could be used.

Case report

A 58-year-old patient with arteriopathy was referred with an exposed Dacron® (du Pont) prosthesis. In the past he had had several operations to improve his intermittent claudication including, in 1974, an aortobifemoral graft. This operation had improved his symptoms until 1983 when he developed claudication in the right leg following occlusion of the right limb of the graft. A right axillofemoral prosthesis temporarily improved his symptoms until 1986 when a right below-knee amputation became necessary. In July 1987, the patient had a right-to-left femorofemoral cross-over graft to overcome an occlusion of the left limb of his bifurcated graft. The wound in his left groin failed to heal resulting in an exposed arterial prosthesis. Several attempts to close the wound were unsuccessful.

Previous abdominal incisions and the state of his arterial tree prevented the use of the usual flaps available for achieving cover of a groin defect. A tissue expander was, therefore, placed in the anterolateral aspect of the thigh in a suprafascial pocket through a new incision. This was rapidly expanded to a volume of 450 ml in 2 weeks, the interval of expansion being from 24 to 48 h (*Figure 1*). When enough skin expansion had been achieved, the graft was mobilized from its bed and the wound was debrided. The sartorius muscle was detached from its origin and transposed over the graft to provide insulation and protection in the event of wound breakdown. Finally, the expanded skin was advanced to permit tension-free closure.

The arterial prosthesis, which was patent at the end of the procedure, failed 48 h later. Re-exploration revealed a thrombus at the origin of the cross-over graft and in the right limb of the bifurcated graft. Despite several attempts to re-establish flow, the patient required a below-knee amputation and was subsequently discharged from hospital.

Discussion

Under normal circumstances, the following muscle or myocutaneous flaps could have been transposed to cover a groin defect. The rectus abdominis muscle, based on the inferior epigastric artery, is normally ideal but this vessel had been transected in the course of previous surgery. The integrity of the medial and lateral circumflex arteries could also not be relied upon, thereby making the use of the gracilis, tensor fasciae latae, rectus femoris and vastus lateralis muscles unattractive. However, on elevating the sartorius muscle in the present case, there was gratifying bleeding from its cut surface and hence this muscle was used to insulate the prosthesis.

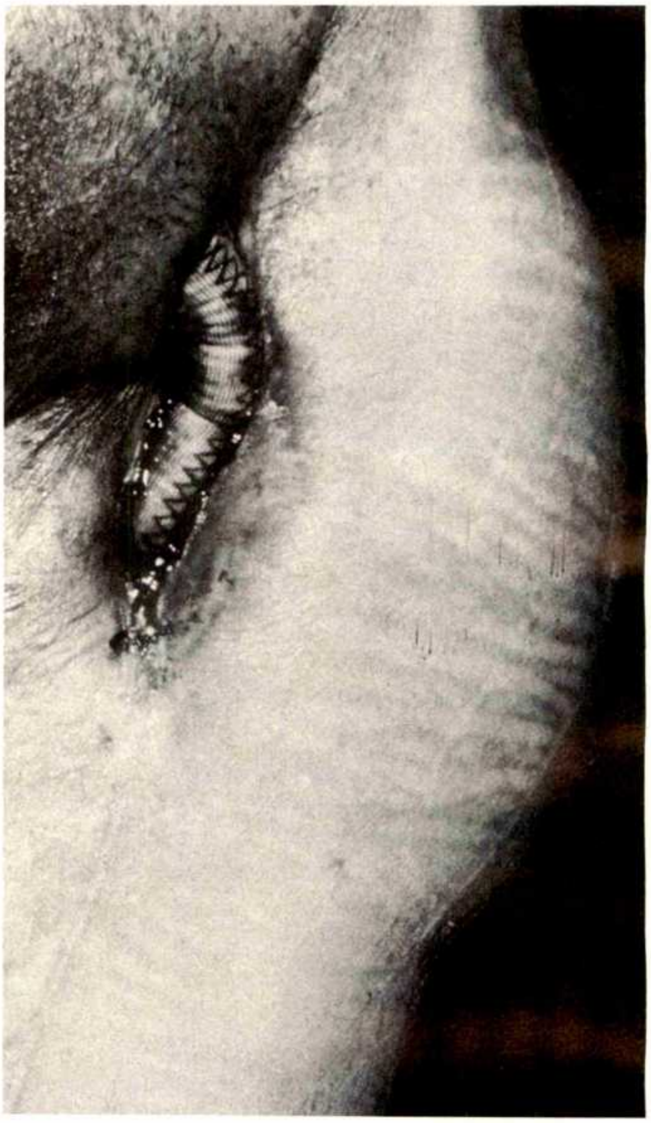

Figure 1 *Left groin: exposed arterial prosthesis and neighbouring dome of expanded skin*

In this case, a tissue expander provided 'extra' skin[6–8] and enhanced the viability of the flap ('delay phenomenon'). The mechanism of 'delay' is an increase in flap vascularity by vessel reorientation and hypertrophy, with metabolic adaption of the flap in response to surgical interruption of a portion of its blood supply[9,10].

We doubt that closure of the wound with an expanded skin flap contributed significantly to eventual graft failure. We feel that in the present case, where there was no alternative, tissue expansion was a good option, allowing closure of the groin wound with neighbouring skin without the added problem of donor site morbidity.

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Surgical workshop

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Délorme operation for prolapsed colostomy

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Stomal prolapse is a complication more frequently found in loop than end colostomies. It can be large enough to make appliance fitting difficult and to make an unsightly bulge.

The principles of Délorme's procedure originally described for rectal prolapse were used in two patients with colostomy prolapse with satisfactory results.

Surgical technique[1]

Under general or local anaesthesia the prolapse is fully extended using Babcock forceps and sufficient 1:400000 adrenaline solution is injected submucosally to elevate all the exposed mucosa (*Figure 1*). This facilitates dissection in that plane and greatly reduces bleeding. A circumferential mucosal incision is made 10–15 mm from the mucocutaneous junction (*Figure 2*). The mucosa is then dissected from the muscularis to the apex of the prolapse. Six to eight plicating sutures of an absorbable material (our preference is for No. 1 polydioxone, Ethicon Ltd., Edinburgh, UK) are inserted in the muscular wall of the colostomy between the mucosal cut edges at the mucocutaneous junction and the apex (*Figure 3*). The sutures are then tied forming a doughnut-like mass which is reduced gently. The mucosal sleeve is then divided and the cut ends of the mucosa are sutured together with 3/0 catgut (*Figure 4*).

Two patients with prolapsed colostomies were successfully treated using this technique. One patient was a 64-year-old woman with a 15 cm long prolapsed permanent left iliac end colostomy. The other was an 84-year-old woman with a 30 cm prolapse of both limbs of a permanent right transverse loop colostomy. The former was treated in February 1985 and the latter in February 1988. Both patients were satisfied with the result of the operation and to date both patients have less than 2·5 cm of prominent mucosa.

Discussion

Colostomy prolapse is a complication with an overall incidence of 2·4–26 per cent[2]. Various methods have been advocated to treat this condition. In terminal colostomy the traditional approach is to excise and reconstruct the colostomy. A simpler procedure is to amputate the redundant bowel but this may be complicated by gangrene of the mucosal cuff and damage to an associated enterocoele[3]. Goligher mobilized the prolapsed colostomy at the mucocutaneous junction dividing it at a point 12–18 mm beyond the anterior abdominal skin and then sutured the cut end of bowel to the skin[4]. Recently Corry described a simple method using a subcutaneous pericolostomy suture

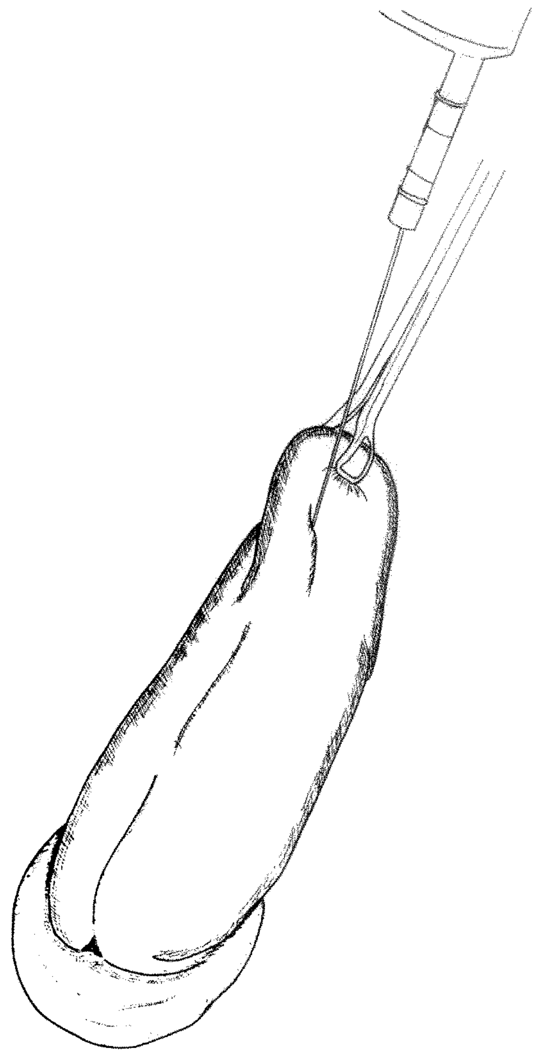

Figure 1 *The submucosal layer is infiltrated with a solution of saline and adrenaline to facilitate the mucosal dissection*

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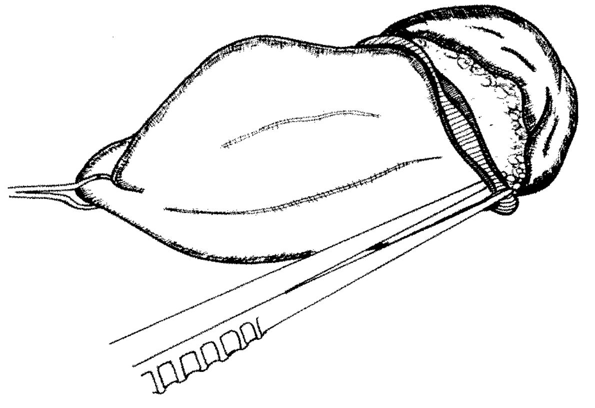

Figure 2 *An incision is made circumferentially around the mucosa 10–15 mm from the mucocutaneous junction, and the mucosa dissected proximally*

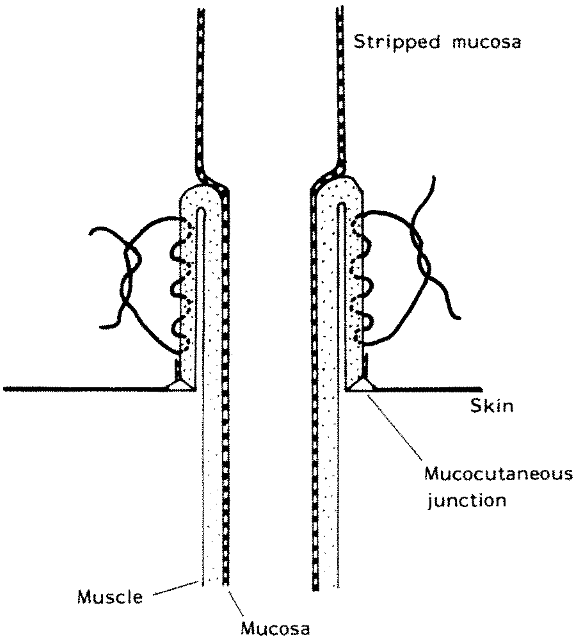

Figure 3 *When the mucosa has been stripped away from the muscle, 6–8 plicating sutures are inserted*

applying the same principle as that of the Thiersch operation for rectal prolapse[5].

Loop colostomy is usually temporary and prolapse is best treated by closure of the colostomy when the circumstances for which the loop was raised are passed. In the rare situation where the stoma is permanent, the loop can be divided fashioning a single barrelled proximal stoma and closing the distal end which is returned into the abdomen.

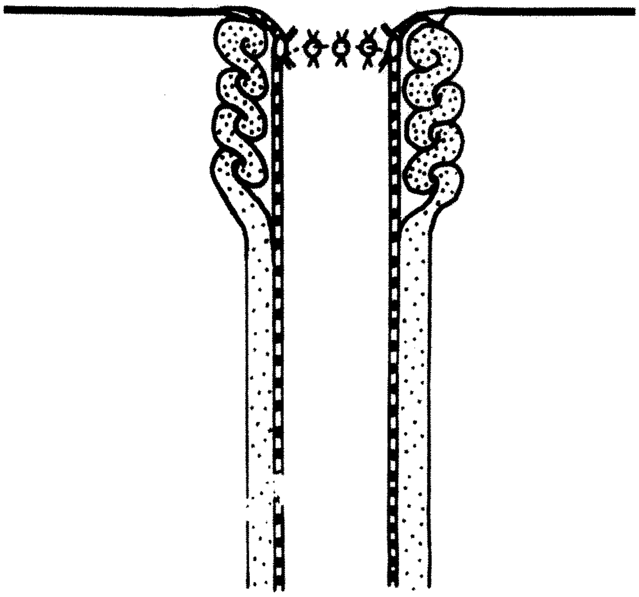

Figure 4 *After reduction of the hernia, the mucosal edges are sutured with interrupted stitches*

Délorme's repair is a simple and effective means of treating prolapsed colostomy, as in our two cases: one of these has been followed up for 3 years, with no significant recurrence. The mucosal protrusion of less than 2·5 cm in both patients did not affect appliance fitting and both were unaware of its presence. We feel it should be considered in elderly and unfit patients not suitable for major surgery. Any late recurrence could be treated with a further Délorme's procedure.

Acknowledgements

We gratefully thank Sister D. Reid and Sister I. Benrad for their assistance in providing the illustrations.

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Prospective comparison of preoperative imaging and intraoperative ultrasonography in the detection of liver tumors

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*A prospective evaluation of the accuracy of preoperative computed tomography (CT), ultrasonography (US), and angiography was performed in 54 patients undergoing resection of hepatic neoplasms. The results were compared with surgical findings and intraoperative ultrasonography (IOUS). A total of 167 lesions was seen by means of IOUS, of which preoperative US enabled detection of 127 (76%). In 48 patients CT allowed detection of 91 of 150 lesions (61%), and in 35 patients angiography showed 56 of 107 lesions (52%). When the detection rate is analyzed according to hepatic segment, the greater overall accuracy of preoperative US may be attributed to a markedly better detection rate in lateral segment of the left lobe of the liver. Lesion size also represented a factor, with preoperative US allowing detection of a greater number of small (less than 2 cm) lesions compared with CT. In patients studied with both CT and US, the combined lesion-detection rate increased to 81% in the right lobe and 76% in the left lobe. Because of this we recommend that preoperative assessment include both CT and US evaluation of the liver. IOUS showed 25% to 35% additional lesions compared with preoperative US and CT. More importantly, 40% of the lesions demonstrated by IOUS were neither visible nor palpable at surgery. We recommend that IOUS be considered in all patients in whom resection of hepatic neoplasm is planned. (*SURGERY *1989;106:849-55.)*

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SEVERAL PREVIOUS STUDIES have compared the relative accuracy of computed tomography (CT), ultrasonography (US), and angiography in detecting hepatic tumors.[1-8] Earlier comparative studies have indicated that CT is the most accurate modality. However, there is recent evidence to suggest that US is more sensitive in the detection of small tumors.[9] This study is a prospective series comparing preoperative CT, US, and angiography to surgical findings and intraoperative ultrasonography (IOUS) of the liver. With this approach, a better assessment of the accuracy of these preoperative imaging modalities may be obtained, as well as an evaluation of the utility of IOUS.

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11/56/15777

MATERIAL AND METHODS

Fifty-four patients undergoing planned hepatic resection with concomitant IOUS during March 1985 through May 1987 were included. The majority of these patients were referred for surgical treatment of metastatic colon carcinoma. A smaller number of patients with other metastatic cancers to the liver, as well as primary hepatic tumors, were also studied. These included four hepatocellular carcinomas, one cholangiocarcinoma, and one metastatic glucagonoma. The patients were examined preoperatively with a combination of CT, US, and angiography. The size, number, and segmental location of lesions were recorded and compared with the findings of IOUS, as well as surgical palpation and inspection. Also noted were other findings, such as vascular invasion and extrahepatic disease.

Preoperative ultrasonograms were taken with an annular array (Technicare, Lewiston, Pa.) or a

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Table I. Accuracy of lesion detection by hepatic segment (%)

Lobe/segment	*Preoperative US*	*CT*	*Angiography**
Right lobe, anterior segment	80.3	71.4	—
Right lobe, posterior segment	73.1	78.9	—
Right lobe, total	77.5	74.4	65.7
Left lobe, medial segment	68.4	52.9	—
Left lobe, lateral segment	77.5	28.9	—
Left lobe, total	74.5	33.6	23.5
Right & left lobe, total	76.0	60.6	52.3

*Lesion detection by angiography was scored by lobe only.

mechanical sector scanner (DRF400; Diasonics, Inc., Milpitas, Calif.), with use of both 3.5 and 5 mHz transducers. The liver was examined with the patient in supine and left lateral decubitus positions. Transverse and sagittal views were obtained using both subcostal and careful intercostal scanning. When needed, the examination was expanded to include upright views for better visualization of the dome of the liver and intercostal scanning with 5 mHz transducer to image the periphery of liver. The routine study also included evaluation of pancreas, kidneys, spleen, celiac, periportal and mesenteric lymph nodes, and retroperitoneum. Preoperative CT evaluation at our institution was performed with a scanner (GE8800; General Electric Co., Milwaukee, Wis.), with use of 1 cm contiguous slices after the administration of intravenous contrast material by multiple bolus injections. The initial bolus consisted of 50 ml of Renograffin 60, followed by two 25 ml boluses. Sequential scans were obtained after each bolus. For some patients, CT scans from outside referring hospitals were included in the study. These were from a variety of modern scanners using contrast-enhanced technique. Noncontrast CT scans were only obtained in two patients with a history of contrast reaction. Angiographic evaluation was performed via selective catheterization of celiac, hepatic, and superior mesenteric arteries.

The results of preoperative imaging were compared with IOUS and surgical findings. The IOUS examination was performed by the radiologist after surgical mobilization of the liver. Direct scanning of the liver was accomplished with both 5 mHz and 7.5 mHz intraoperative probes (Aloka 330; Colormetrics Medical Systems, Inc., Wallingford, Conn.). The IOUS examination included demonstration of hepatic vein confluence, inferior vena cava, and the main, right and left portal veins. Lesions known from preoperative imaging were identified and their relationship to adjacent hepatic and portal veins established. The entire liver was then systematically scanned with both 5 mHz and 7.5 mHz probes. Additional lesions were recorded and localized according to hepatic segment. Other findings such as vascular invasion were also noted. The findings were correlated to surgical palpation, as well as visual inspection of surface lesions.

RESULTS

The number of lesions detected by surgical findings and IOUS were compared with the preoperative findings and categorized according to segmental location. The total accuracy of each modality was recorded, as well as the segmental and lobar accuracy distribution. In 54 patients 167 lesions were detected with IOUS, of which preoperative US showed 127 (total accuracy of 76%). In 48 patients preoperative CT showed 91 of 150 lesions seen at IOUS (total accuracy of 60.6%). In 35 patients angiography showed 56 of 105 lesions seen at IOUS (total accuracy of 52.3%).

The surprisingly greater detection rate of preoperative US versus CT scanning is explained when the accuracy is broken down according to hepatic segments (Table I). With preoperative US the accuracy of detection of lesions by segment and lobe are similar (right lobe, 77.5%, versus left lobe, 74.5%). However, the preoperative CT scan shows a significant discrepancy in detection in right and left lobe lesions compared with IOUS (right lobe, 74.4%, versus left lobe, 36.3%). This difference is most pronounced in the detection of lesions in the lateral segment of the left lobe of the liver where preoperative US showed 77.5% of the lesions versus 28.9% by CT scan. This is probably related to decreased CT resolution of left lateral segment lesions due to image degradation by streak artifacts from the stomach and by cardiac motion (Fig. 1). In patients studies preoperatively with both CT and US, the combined detection rate increased to 80.8% in the right lobe and 76.3% in the left lobe. In the fewer number of patients studied with both CT and angiography, the accuracy in the right

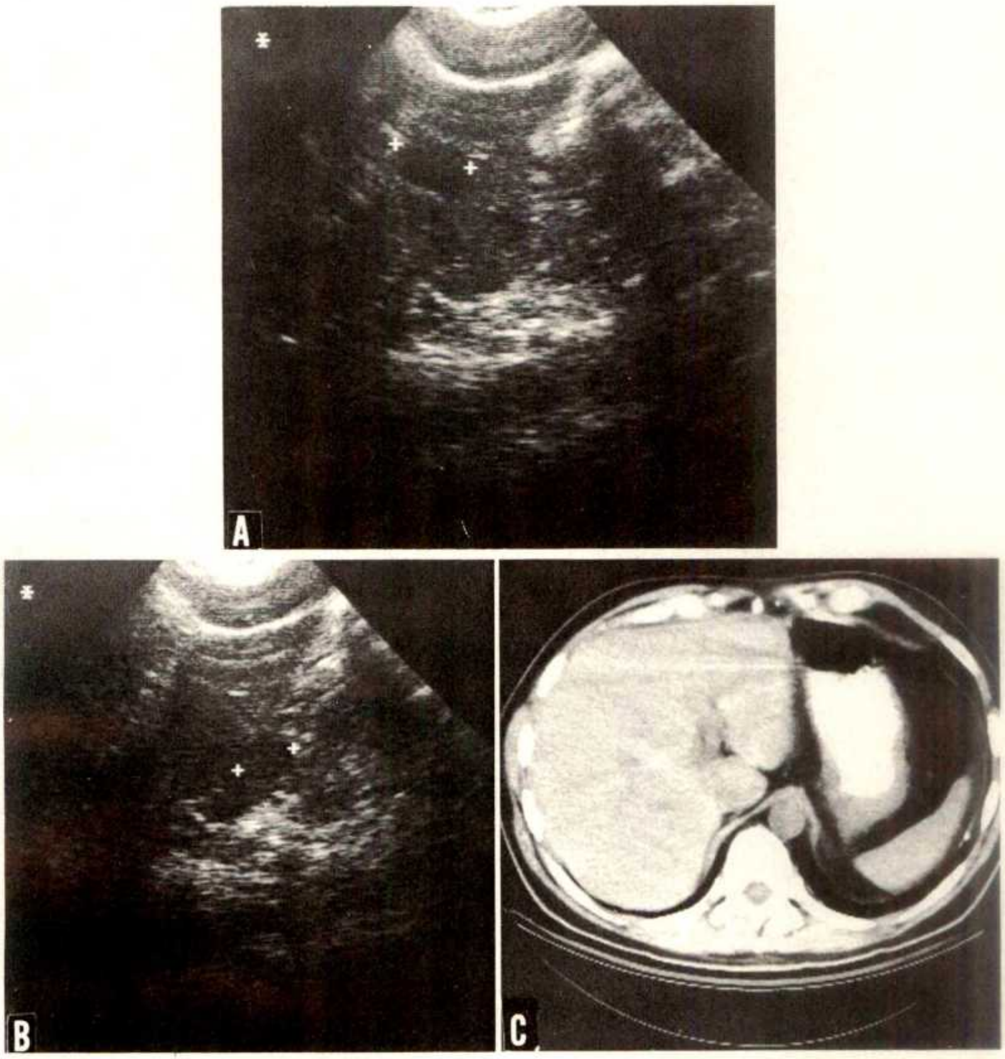

Fig. 1. **A** and **B**, Preoperative US, sagittal views, lateral segment of left lobe shows two hypoechoic masses. **C**, CT scan lateral segment of left lobe, same patient. Above lesions not identified due to streak artifact from stomach.

lobe was similar (78.4%). In the left lobe, however, the combined accuracy was no greater than that of CT alone.

Angiography detected 65.7% of right-lobe lesions and 23.5% of left-lobe lesions. This was attributed to both small lesion size and the hypovascular nature of colonic metastases. Of the 35 angiography patients, six had noncolon primary tumors. Although this represents a small number, the accuracy of detection of lesions in this group increased to 75% in the right lobe and 50% in the left lobe. Tumors missed in this group were small hypovascular lesions.

The detection rate was also influenced by the size of the lesion. Lesions more than 3 cm in diameter were generally imaged by all modalities. Most of the lesions seen by preoperative US and missed by CT scan were small, measuring 1 to 2 cm. In several cases IOUS showed lesions less than 1 cm in diameter that were not visible preoperatively by any modality (Fig. 2). Forty percent of the lesions seen with IOUS were neither visible nor palpable in surgery.

In the case illustrated in Fig. 2, C, IOUS showed multiple small lesions in the right lobe in addition to the two lesions in the left lobe, seen with preoperative imaging. The planned left hepatic lobectomy was not performed because of the bilobar involvement. The

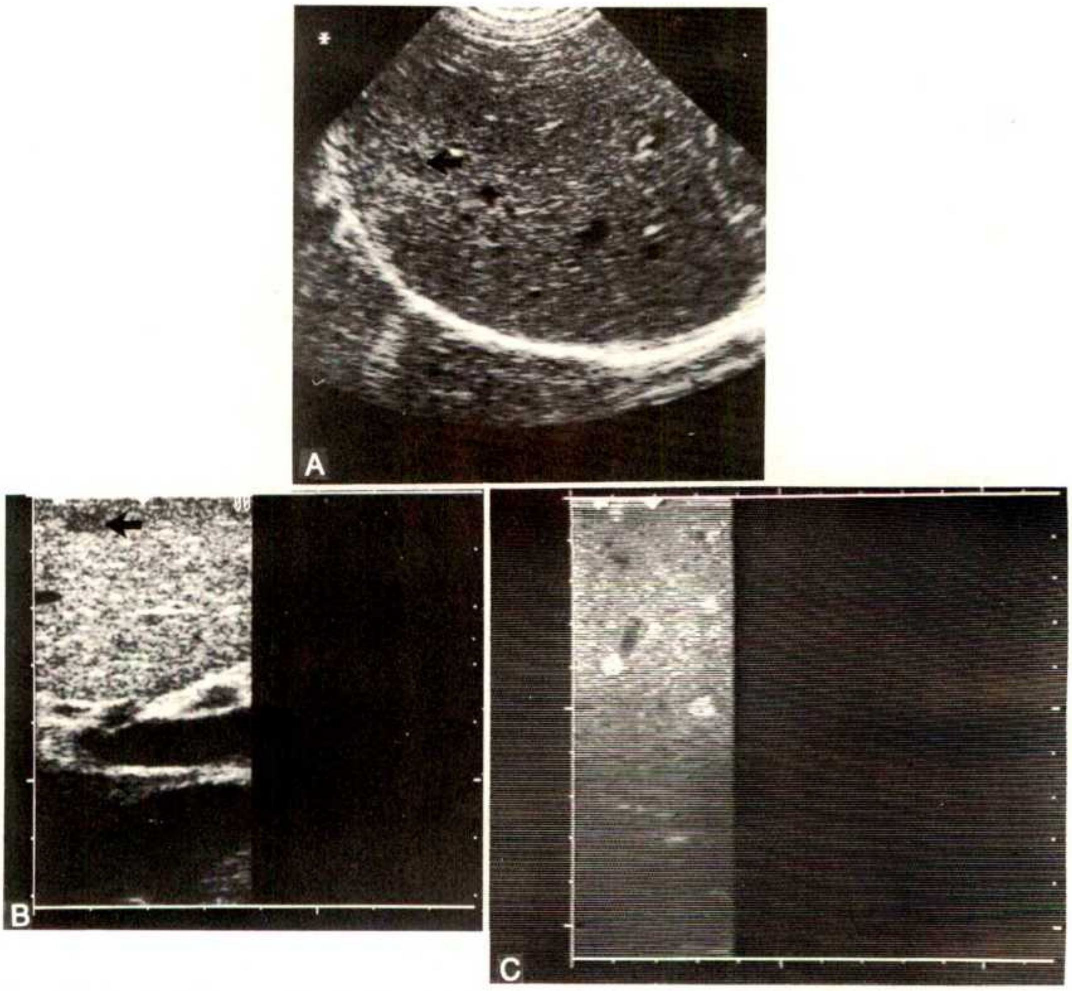

Fig. 2. A, Preoperative US, sagittal view, right lobe shows 1 cm metastatic lesion *(arrow)*. **B,** Despite preoperative visualization of small (1 cm) lesion above, IOUS showed additional lesion, measuring 5 mm in diameter *(arrow)*. **C,** Different patient. Superior resolution of IOUS shows multiple echogenic lesions measuring 5 mm and less in diameter, not seen preoperatively.

right lobe lesions were followed up and found to increase in size. A biopsy specimen was positive for tumor.

Of the 54 patients, six had tumors deemed unresectable at surgical exploration because of extent of hepatic disease or evidence of extrahepatic spread of tumor. IOUS showed the lesions of an additional five patients to be unresectable on the basis of extent of tumor involvement of both lobes, which was not evident preoperatively. In another 17 patients the findings of IOUS altered the surgical plan. These findings included localization and discovery of new lesions and demonstration of extent of vascular invasion by tumor. For example, the preoperative plan of lobectomy could be altered to an extended lobectomy or trisegmentectomy to include new lesions discovered with IOUS. In addition, tumors amenable to wedge resection could be accurately localized. In some cases, IOUS-monitored cryosurgery of lesions was performed in conjunction with resection.[10] Thus the findings of IOUS changed the surgical plan in 32% of the patients studied.

DISCUSSION

IOUS is currently performed in many institutions as an adjunct to hepatic resection. The information provided by this procedure has influenced surgical planning and encouraged a reevaluation of preoperative diagnostic imaging. The greater detection rate of preoperative US versus CT demonstrated in our study is in contradistinction to many reports. However, the accuracy of

Table II. Review. Accuracy of preoperative imaging vs IOUS (%)

Study	*Preoperative US*	*CT*	*Angiography*
Sheu 1985	89.6	85	82
Gunven 1985	66.0	80	52
Castaing 1986	68.0	67	40
Gozzetti 1986	80.4	74	—

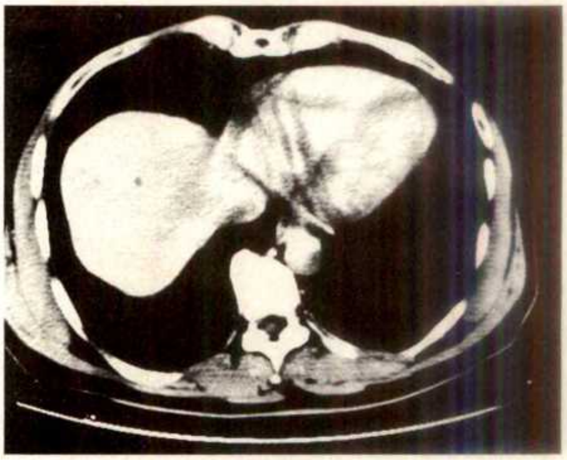

Fig. 3. CT scan, dome of right lobe of liver. Metastatic lesion and small cyst not seen on preoperative US.

IOUS versus preoperative imaging in both primary and metastatic neoplasms has been compared in recent literature (Table II). One study (Gozzetti et al., 1986), demonstrated a greater accuracy of preoperative US (80%) versus CT scan (74%), in agreement with our findings.[11] In a study restricted to hepatocellular carcinomas of less than 5 cm in diameter (Sheu et al., 1985), the accuracy of preoperative US again surpassed CT scanning.[12] Castaing et al.[13] reported an equal accuracy of preoperative CT and ultrasound. Another (Gunven et al., 1985) agrees with the previusly reported greater accuracy of preoperative CT compared with US and angiography.[14] As in older studies, the preoperative US examinations in this case were performed with static gray scale scanners rather than current real-time technology. This most likely contributed to the lower accuracy of preoperative US since complete assessment of liver parenchyma requires the flexibility of real-time US, especially for upright and decubitus subcostal and intercostal scanning.

Analysis of the detection rate of each modality by hepatic segments provides insight into the cause of the discrepancy. CT has the lowest detection rate in the left lobe of the liver, particularly the lateral segment. Images of this area are frequently degraded by cardiac motion and by streak artifacts related to the stomach or transverse colon. CT is slightly more accurate in detecting lesions in the dome of the liver and lateral costal margin, areas which can be difficult to fully assess by US (Fig. 3). Angiography is also limited in the left lobe, particularly with small or hypovascular lesions, because of the overlapping spinal column.

The size of lesions also represents a factor in determining accuracy of detection. Small lesions measuring 1 to 2 cm in diameter are best seen with US. Because of slice thickness, volume averaging, and respiratory motion, these lesions could be partially imaged or missed by CT. All preoperative imaging modalities missed the presence of small surface lesions that were visible only at surgery.

In one case of hepatocellular carcinoma, a diffusely infiltrating lesion was missed prospectively with a contrast and noncontrast CT scan. US showed tumor present in both lobes of the liver, as well as invasion of the portal vein (Fig. 4). This suggests that US may have an advantage in imaging infiltrating neoplasms by the detection of heterogeneous liver texture and architectural abnormalities that may not present as focal lesions on CT scan. Although both US and angiography show vascular invasion, US can show tumor within veins that are not opacified at angiography.[15] However, only with angiography can one identify arteriovenous shunting. CT is considered less accurate in showing tumor invasion of the venous structures.[16] In our series, there were two cases of venous invasion—one into the portal vein and the other into the inferior vena cava. Invasion of the inferior vena cava was seen with both CT and US, whereas the portal vein invasion was seen only with US.

Of interest is the incidental finding by preoperative US of three renal masses, each measuring approximately 2 cm in diameter. These consisted of one angiomyolipoma and two renal cell carcinomas. One of the renal cell carcinomas was missed with a noncontrast CT scan. The other renal cell carcinoma was an exophytic lesion, extending from the lower pole of the left kidney, and was not included on the contrast CT scan of the liver.

The use of IOUS has become increasingly important in hepatic resection for depiction of liver anatomy and localization of tumors to specific lobes and segments. It has facilitated the detection and biopsy of small lesions and demonstrated the relationship of tumors to major intrahepatic vessels. The information provided by IOUS

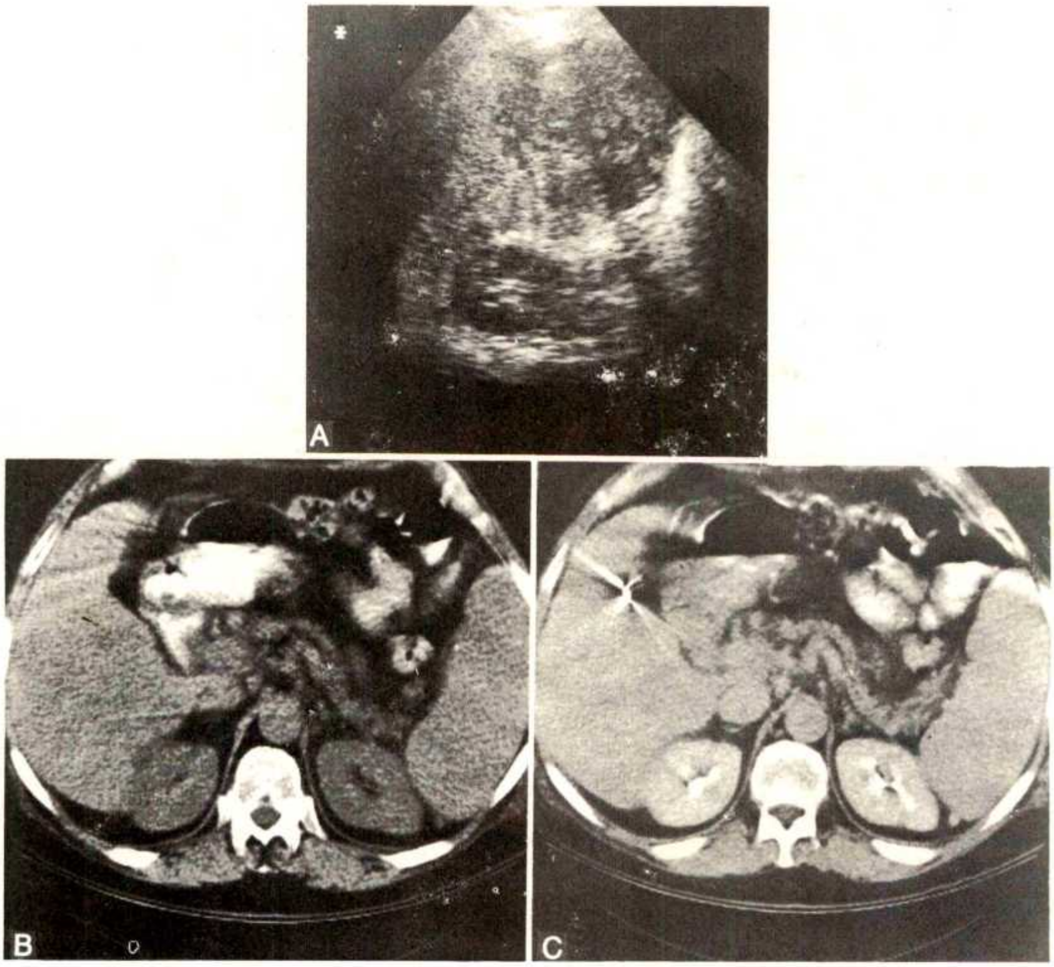

Fig. 4. A, Preoperative US, transverse view, right lobe shows 6 cm hepatocellular carcinoma. Prospectively, mass not visualized on noncontrast and contrast CT scan (**B** and **C**).

may alter the operative plan to extend or limit a resection or may indicate nonresectability.[11, 12, 17] The impact of IOUS was demonstrated in our study in that the operative plan was changed in one third of the patients. IOUS of the liver has been used extensively in the surgical biopsy and resection of hepatocellular carcinomas. It has proved indispensable in the localization and biopsy of small multifocal lesions, particularly in a cirrhotic liver. In one third of cases, these lesions were neither visible nor palpable at surgical exploration.[12] This was confirmed by our study in which 40% of lesions were neither visible nor palpable at surgery. In cirrhotic livers, IOUS can guide subsegmental resection of such lesions in order to preserve as much hepatic parenchyma as possible.

Several conclusions have been drawn from our comparison of preoperative imaging modalities. Although angiography is efficacious in showing hypervascular hepatic masses, there is a decreasing role for angiography in the diagnosis of hypovascular colonic metastases. It should be performed when the surgeon requires a vascular road map or when placement of a hepatic arterial catheter for chemotherapy infusion is planned. The additive effect of preoperative evaluation with CT and US resulted in a lesion-detection rate of 80.8% in the right lobe and 76.3% in the left lobe. Because of this, we recommend that preoperative assessment of liver tumors include both CT and US. With evolving technologic advances in imaging—including CT angiography and newer-generation US and CT scanners, with improved resolution and scanning time—the preoperative accuracy can only increase. Although our current series does not include magnetic resonance imaging, future study will be directed to comparison of MRI to preoperative and intraoperative US.

Forty percent of lesions detected by means of IOUS in our study were not visible or palpable at exploration. Because of this finding and the impact of alteration of the surgical plan in one third of the patients, we recommend that IOUS be performed in patients undergoing surgical treatment of hepatic neoplasm.

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Surgical Research Society Abstracts

The 70th Meeting of the Surgical Research Society, organized by the London Hospital Medical College was held at the University of Newcastle on the 6th and 7th July 1989.

Immunomodulation of lymphocytes following circulation through colorectal carcinomas

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Malignancy is associated with depression of the host immune response. To determine if passage of lymphocytes through a carcinoma affected their number and function, 26 patients undergoing surgery for colorectal cancer were studied. Blood was sampled from the artery supplying and the vein draining the tumour. Separated lymphocytes were stained with a panel of monoclonal antibodies for T and natural killer (NK) cell subpopulations, along with basal and stimulated interleukin 2 receptor (IL-2R) expression. Lymphocyte transformation (LT) to the T cell mitogen phytohaemagglutinin was assessed by measuring uptake of tritiated thymidine. NK cell activity (percentage killing) was determined using a 4-h ^{51}chromium release cytotoxicity assay with K562 cells as the target.

	NK (%)	Percentage killing	Basal IL-2R	Stimulated IL-2R	LT c.p.m $\times 10^3$
Arterial	27(11–60)	19(3–57)	6(1–30)	76(35–91)	30(4–81)
Venous	35(12–60)*	23(8–42)	6(2–22)	70(31–88)	12(2–72)†

Results expressed as median (range). Significance *versus* arterial *$P<0\cdot002$, †$P<0\cdot02$ (Wilcoxon paired ranks sum test)

The percentage of NK cells was significantly increased in the venous blood draining the tumour compared with the arterial inflow, but overall NK cell activity was unchanged. There were no differences in the T cell subpopulations. Lymphocyte transformation was decreased in the tumour draining blood compared with arterial blood, but IL-2R expression was unaltered. These data suggest that local effects of colorectal cancer may include the ability to down-regulate T cell function, but increase NK cell number. Means of enhancing this antitumour activity therapeutically, possibly by infusion of immunomodulating agents into the portal vein intraoperatively, need to be considered.

Why do women develop breast cysts?

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No risk factors for the development of breast cysts have been described[1]. Follow-up of a group of 639 women with benign nodularity has shown an excess risk of breast cancer among cyst formers alone[2] This study examined whether the risk factors for breast cysts and breast cancer are the same. We have determined prospectively the risk factors for clinically palpable cysts in women seen between 1976 and 1982 in the breast clinic. In all, 352 women developed cysts and 287 had benign nodularity. Univariate analysis showed that age ($\chi^2=140$, $P<0\cdot001$), age at first live birth ($\chi^2=17\cdot54$, $P=0\cdot00015$), older age at menarche ($\chi^2=14\cdot9$, $P=0\cdot0049$), (bra size ($\chi^2=17\cdot68$, $p=0\cdot007$) and shorter duration of contraceptive pill use ($\chi^2=46\cdot56$, $P<0\cdot001$) were all significantly associated with cyst formation whereas smoking, breast feeding and parity were not. Cyst formers were less likely to be current users ($P<0\cdot0001$) or 'ever' users of the pill ($P<0\cdot0001$). Multiple regression analysis revealed three independent factors in predicting cyst formation age ($P<0\cdot0001$), duration of pill use ($P=0\cdot0009$) and bra size ($P<0\cdot002$). The oral contraceptive protects women from development of breast cysts Late age at first live birth is the only recognized risk factor that cyst formers share with breast cancer patients. We conclude that breast cyst formation has a different mechanism from breast cancer development.

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Prospective trial of University of Wisconsin solution compared with Marshall's solution for human hepatic allograft preservation

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A new liver allograft perfusion fluid (University of Wisconsin solution, UW) is reported to allow longer preservation than other solutions in animals[1] and humans[2], with good graft function; results of comparative studies are awaited. We report the first, single centre, controlled trial comparing UW to Marshall's solution in hepatic allograft preservation.

Donors were randomized prospectively to receive Marshall's or UW solution. Liver function was assessed by the peak serum aspartate transaminase (AST) and peak prothrombin time (PT) in the first 3 days and on day 7 (AST 7, PT 7) and by biochemical liver function tests at 1 and 3 months. The donor groups were similar for age, cause of brain death, and duration of ventilation. The recipients' ages, genders and diagnoses were comparable.

	UW solution ($n=37$)	Marshall's solution ($n=32$)
Ischaemic time (min)	705 (253–1107)*	346·5 (195–687)
Peak AST (units/l)	748 (135–7000)	771 (210–10 000)
AST 7 (units/l)	47 (13–4011)	65 (18–2829)
Peak PT (s)	31·5 (19–142).16	32 (20–148):16
PT 7 (s)	20 (13–106):16	18 (14–48) 16

Results expressed as median (range) *$P<0\cdot001$ Wilcoxon's two-sample test

Differences in mortality and irreversible graft damage rates were not significant. No side-effects due to UW solution occurred. At 3 months the serum bilirubin in the UW group was 27 *versus* 17, $P<0\cdot05$. This research continues but results suggest that UW solution is at least as effective for hepatic allograft preservation as Marshall's solution despite significantly longer preservation periods.

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Does iloprost benefit the patient with claudication? Results of a double-blind placebo-controlled trial

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Iloprost, a stable prostacyclin analogue, has been evaluated in a double-blind placebo-controlled cross-over trial. Thirty-eight patients with stable claudication (33 male, five female; mean age 63 years, range 41–79) were given iloprost or placebo and then crossed over after 3 months. Daily 7·5-h intravenous infusions were given for 3 days on each occasion at a maximum dose of $2\,\mathrm{ng\,kg^{-1}\,min^{-1}}$. Subjective response, claudication distance (CD), maximum walking distance (MWD), systolic pressure ratios and maximum hyperaemic limb blood flow (LBF) measured with an isotope[1] were recorded before each treatment and then regularly for 3 months.

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Twenty patients (53 per cent) found iloprost more effective than placebo and two (5 per cent) found placebo more effective than iloprost. Sixteen patients (42 per cent) had no benefit from either treatment. Below are percentage changes from baseline values, showing significant differences between the iloprost and placebo groups (Mann–Whitney *U* test, $^*P<0·05$, $^†P<0·001$).

	CD*	MWD*	LBF (1 day)*	LBF (3 months)†
Iloprost (%)	+74	+80	−7·9	−5·8
Placebo (%)	+35	+44	−5·2	+12·9

The subjective and objective improvements in performance are associated with a fall in hyperaemic blood flow that persists for 3 months after iloprost but recovers after placebo. Iloprost may induce a metabolic adaptation to arterial occlusion which warrants further investigation

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Mucosal blood flow following restorative proctocolectomy: pouchitis is associated with mucosal ischaemia

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Restorative proctocolectomy and pouch anal anastomosis provides a means of eradicating disease in ulcerative colitis whilst preserving normal anal function. However, 5–30 per cent of patients develop 'pouchitis', an inflammatory condition associated with diarrhoea, contact bleeding and ulceration on sigmoidoscopy with histological appearance of neutrophil infiltration. As there are occasional difficulties in delivery of the pouch to the pelvis due to inadequate mesenteric length, we have investigated the possibility that pouchitis might be due to pouch ischaemia.

Using the Pf2® (Perimed, Sweden) laser Doppler probe passed via the biopsy channel of a flexible sigmoidoscope, we compared mucosal blood flow in patients following restorative proctocolectomy ($n=14$) and controls with an ileostomy ($n=12$). Multiple flux readings were obtained from the four quadrants of the pouch, the distal ileum above the pouch and from ileostomies. Flux in the pouch (mean 0·88 v, range 0·25–1·8 v) was significantly lower than in healthy ileostomies (1·9 v (0·6–2·7)) ($P<0·01$, Mann–Whitney *U* test). In patients with pouchitis ($n=6$) the flux reading (0·45 v (0·25–0·5)) was significantly lower than in patients with macroscopically normal mucosa ($n=8$) (1·0 v (0·6–1·8)) ($P<0·05$, Mann–Whitney *U* test). There was no significant difference in the flux of J pouches compared with W pouches.

These results suggest that ischaemia may be an aetiological factor in the pathogenesis of pouchitis.

Effect of photodynamic therapy on swine ureters and colonic anastomoses

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Photodynamic therapy (PDT) is a technique in which a photosensitizing drug (haematoporphyrin derivative (HpD) can be activated by laser light to kill tumour cells selectively. One exciting application would be the intraoperative adjunctive treatment of residual tumour after excision. Before it could be used in humans, however, the effect on normal tissues needs to be determined. We have investigated intraoperative PDT effects on ureters and colonic anastomoses, structures which would be irradiated after rectal cancer resection. Twenty-four miniature piglets (weight 16–51 kg) were given HpD 5 mg/kg 48 h before laparotomy. Eight piglets each received two colonic transections and anastomoses, one receiving ambient light only and the other 40 J/cm² 460–580 nm light delivered from a 600 W tungsten halogen light source passing through a water bath and waveband filter. Nine piglets had a 3-cm ureter illumination with the same light dose. Anastomoses were assessed at 8 days and ureters at 6 weeks by Whitaker's test and measurement of cross-sectional areas (CSA) of biopsies by a computer-based image analysis system with customized software.

	Control*	PDT*
Colon ($n=8,8$)		
Bursting tension (N/cm)	70·2 (60·6–82·5)	76·0 (52·8–85·2)
Hydroxyproline (μg/mg)	14·8 (12·8–17·3)	15·3 (13·8–17·2)
Water content (%)	81·0 (80·1–82·8)	82·7 (80·9–84·7)
Ureter ($n=17,10$)		
Whitaker (cmH_2O)	12·3 (9·0–15·6)	11·6 (7·0–12·5)
Ureter diameter (mm)	2·41 (2·2–2·7)	2·56 (2·4–2·7)
CSA lumen ($\times 10^3$ μm²)	42·6 (21·0–70·0)	32·6 (21·3–70·4)

Values are median (interquartile range) *No significant differences (Mann–Whitney *U* test, $P>0·05$)

All anastomoses were macroscopically perfectly healed. Intraoperative adjunctive PDT can safely irradiate normal ureters and colonic anastomoses and this paves the way for its use in humans.

Prognostic significance of marrow micrometastases in women with early breast cancer

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Twenty-five patients with early breast cancer (stages I and II) have been studied prospectively to determine the relationship between marrow micrometastases, disease-free interval and survival. Marrow specimens were aspirated from three sites immediately before breast surgery. An immunocytochemical technique using monoclonal antibody LICR.LON M8.4 was employed to detect micrometastases. The minimum follow-up was 38 months.

Twelve of the 25 patients (48 per cent) had micrometastatic lesions in their marrow at presentation. Four of these patients developed distal recurrence during follow-up, causing death in two of them. Five of the 13 patients with no evidence of micrometastases developed distant recurrence and four of them have died.

There was no correlation between the state of the marrow and the development of metastatic disease, although both axillary lymph node status and tumour volume correlated significantly with outcome (both $P<0·025$).

Micrometastatic lesions appear to be common in the marrow of patients with early breast cancer. We have been unable to demonstrate that they have prognostic significance.

Effect of blood in the field of pulsed laser ablation of atherosclerotic tissue

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Selective ablation of atheroma can be achieved using a 1 μs pulsed dye laser at short wavelengths[1]. During *in vivo* lasing, blood is present in varying quantities between the optical fibre delivery device and the arterial wall. This work explores the effect of the presence of blood on wall penetration and perforation times. Six samples from each of eight normal and eight atheromatous cadaver femoral arteries were subjected to laser energy via a 600-μm diameter quartz fibre held perpendicularly to the wall with a 50 g loading. Laser energy was applied under heparinized saline, whole blood and blood in 1:2 and 1:4 dilutions. The end-point of the experiment was taken as the time to wall perforation. The mean (s.d.) perforation times in s for normal and atheromatous wall at 100 mJ are shown in the *Table*

Tissue	Saline	1:4 dilution	1:2 dilution	Whole blood
Normal wall	9·8 (1·6)	4·3 (0·9)	3·0 (0·5)	1·9 (0·3)
Atheroma	4·2 (0·9)	2·0 (0·7)	1·3 (0·3)	1·0 (0·2)

Blood between the fibre-tip and the arterial wall significantly increases the rate of penetration through both normal artery and atheromatous wall ($P<0·002$, Student's *t* test). The preferential absorption by atheroma compared to normal wall is maintained

($P<0.01$). Haemoglobin strongly absorbs blue-green light and may lower the threshold for the production of the plasma produced by short-pulsed lasers Given careful monitoring of the position of the fibre-tip, the presence of blood, even when diluted by heparinized saline, will therefore improve the efficiency of laser recanalization of a blocked vessel.

1. Murray A, Crocker PR, Wood RFM. The pulsed dye laser and atherosclerotic vascular disease *Br J Surg* 1988, **75**. 139–41.

A controlled clinical trial comparing low dose heparin with low molecular weight heparin in the prevention of deep venous thrombosis

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Low dose heparin is the standard treatment for the prevention of postoperative deep venous thrombosis but there is now increasing evidence that low molecular weight heparins are an effective and safe alternative to low dose heparins. The aim of this study is to investigate the use of a new low molecular weight heparin (Logiparin) in the prevention of postoperative deep venous thrombosis in a multicentre controlled study

General surgical patients were randomized into three groups. (a) standard heparin (5000 units twice daily); (b) Logiparin (2500 units daily), and (c) Logiparin (3500 units daily) Daily ^{125}I-labelled fibrinogen uptake tests were performed from day 2 to day 7 to detect deep venous thrombosis.

A total of 1290 patients were entered into the study. There was no significant difference in the incidence of positive leg scans in the standard heparin (4·2 per cent, $n=429$) compared with the 3500 units Logiparin group (3 7 per cent, $n=430$), but the incidence of deep venous thrombosis was significantly higher in the 2500 units Logiparin group (7 9 per cent, $n=431$). There was no significant difference in the incidence of severe haemorrhages or the rates of major complications (death, pulmonary embolism, reintervention) in the three groups This study shows that Logiparin, at a dose of 3500 units daily, is a safe and effective means of preventing postoperative deep venous thrombosis in general surgical patients

Timing of antibiotic administration in limb surgery under tourniquet

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In limb surgery isolation of the operative site by tourniquet deprives the distal tissues of oxygenated blood and systemic antibiotic. In addition sequestered haematoma following tourniquet release is an ideal site for infection if systemic antibiotic concentration is too low Infection of implanted material is a major complication of limb surgery which may eventually lead to amputation. We have investigated the timing of antibiotic administration in 29 patients undergoing 32 total knee replacements under tourniquet. Patients were randomized to one of three prophylactic systemic antibiotic regimens group 1, 1 g cefamandole 5 min before tourniquet application; group 2, 2 g cefamandole 5 min before tourniquet application, and group 3, 1 g cefamandole 5 min before tourniquet application + 1 g cefamandole 2 min before tourniquet release

Antibiotic concentrations were measured in the serum and in the drain fluid from the wound.

	Group 1 ($n=8$)	Group 2 ($n=8$)	Group 3 ($n=16$)
Serum			
Mean peak concentration (μg/ml)	110	249	130
Mean tourniquet release concentration (μg/ml)	42	45	150
Drain fluid			
Mean tourniquet release concentration (μg/ml)	15	23	44

The drain fluid concentration in group 3 was significantly higher than in the control groups 1 and 2 ($P=0.007$ and $P=0.008$ respectively); there was no significant difference between the two control groups. Drain fluid concentration correlated significantly with the serum concentration at the time of tourniquet release ($r^2=0.554$, $P<0.001$)

Systemic antibiotic therapy for patients having limb surgery under tourniquet should include a tourniquet release dose.

Effect of fibrinolytic enhancement on venous ulcer healing

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Lipodermatosclerosis, which is known to precede venous ulceration, improves when treated with elastic stockings and fibrinolytic enhancement[1] Our aim was to discover if fibrinolytic enhancement would promote ulcer healing when combined with weekly compression dressings consisting of Calaband® (Seton Healthcare Group, Oldham, UK), Elastocrepe® (Smith & Nephew Ltd., Hull, UK) and Tubigrip ® (Seton Healthcare Group) bandages. Arterial Dopplers and rheumatoid serology were performed on entry, and foot volumetry after healing. In all, 126 patients with proven venous ulcers were prospectively randomized to receive either 5 mg stanozolol twice daily or placebo, until healed. Randomization was stratified into three groups based on initial ulcer size.

The treatment group consisted of 62 patients of whom 44 healed, seven remained unhealed at 1 year, and 11 were withdrawn for deterioration, non-compliance, or side-effects. Of the 64 taking placebo, 44 healed, 11 remained unhealed at 1 year, and nine were withdrawn. Kaplan–Meier survival curves showed no significant difference between the groups in the time taken to achieve healing. Our compression regimen healed 83 per cent of those patients who complied with treatment, 53 per cent, within 3 months. This provides baseline data against which new dressing regimens can be tested There is no evidence that fibrinolytic enhancement expedites ulcer healing, or significantly increases the percentage that heal.

1. Burnand KG, Clemenson G, Morland M, Jarrett PM, Browse NL Venous lipodermatosclerosis. treatment by fibrinolytic enhancement and elastic compression. *Br Med J* 1980, **280**: 7–11.

Venous ulceration and the microcirculation of the skin in the calf

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The microvascular abnormalities in venous ulceration include a pericapillary fibrin cuff, white cell 'trapping' in the lower limb and possible abolition of microcirculatory reflexes

The aim of this study was to determine whether posture affects the microvascular function in the ankle skin of patients with deep venous insufficiency (DVI), and to assess the postural vasoconstriction reflex in these patients.

Duplex ultrasound assigned 50 subjects to normal (N), superficial venous insufficiency (SVI) and DVI categories. Video capillary microscopy, laser Doppler flowmetry (LDF) and transcutaneous oxygen monitoring (P_{tc,O_2}) were used to assess the microcirculation while subjects lay supine for 30 min and then sat with legs dependent for 30 min Indirect body heating (IBH), releasing sympathetic tone, was instituted for 60 min, and the protocol was then repeated. Statistical analysis was by Student's *t* test

All groups showed a rise in the number of visible capillary loops per unit area on dependency (N, SVI, DVI, $P<0.0001$). The P_{tc,O_2} was lower in the DVI group than the other groups ($P<0.001$), the SVI and N groups showed a rise on dependency (N, $P<0.004$, SVI, $P<0.009$). LDF showed decreased blood flow on dependency in all groups (N, SVI, DVI, $P<0.0001$). IBH did not impair this reflex. None of the measured parameters deteriorated during the dependent period.

The postural vasoconstriction reflex remains intact in the DVI group No evidence of a progressive microvascular deficit due to white cell trapping was observed during the course of this study. IBH shows that arteriovenous shunting has no effect on any of the parameters measured

Double-blind placebo-controlled study of indobufen in intermittent claudication

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Indobufen is a potent oral antiplatelet agent which acts by blocking cyclo-oxygenase. The aim of this study was to assess the value of indobufen in patients with intermittent claudication.

Thirty-three consecutive patients (25 male, eight female, mean age 58 (range 35–72) years), whose intermittent claudication did not improve after 1 month of treatment with placebo were recruited to a double-blind placebo-controlled study of indobufen

Assessment was made using a treadmill test (3·2 km/h 8° slope) assessing initial and maximum claudication distances, pre- and postexercise ankle Doppler studies and radioisotope limb blood flow.

The mean (s.d.) initial claudication distance improved significantly from 90(40)m to 155(132)m on indobufen ($P<0\cdot05$) but not on placebo (82(28)m cf 95(52)m) The maximum claudication distance improved from 168(113)m to 263(188)m ($P<0\cdot05$) on indobufen but not on placebo (122(39)m cf 201(147)m). The improvement in initial (but not maximal) claudication distance was significantly greater with indobufen compared with placebo ($P=0\cdot05$) but Doppler studies and limb blood flows remained unchanged

Indobufen is an effective medical treatment for intermittent claudication

Detection and characterization of arterial thromboses using a platelet specific monoclonal antibody (P256 Fab′)

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Arteriography does not reliably distinguish between acute and chronic arterial occlusions, and does not select those patients likely to benefit from thrombolysis We have investigated ten patients with acute lower limb ischaemia by arteriography and ^{111}In-labelled P256 Fab′ platelet specific monoclonal antibody imaging; 20 MBq ^{111}In-P256 was administered intravenously and patients were imaged after 5 h.

Six patients were treated with intra-arterial thrombolysis Three of these patients had highly positive ^{111}In-P256 uptake, thrombolysis was successful and the vessel remained patent. However, in the three patients with negative images, despite initially successful thrombolysis, immediate rethrombosis occurred in two, only one remaining patent

The remaining four patients were not treated with thrombolysis. Two had positive ^{111}In-P256 images, demonstrating clinically occult bilateral iliac aneurysms with distal embolization in one, and two separate sites of critical stenoses (90 per cent) in the other. In the two patients with negative images, thrombolysis was contraindicated due to the presence of a Dacron® (Du Pont) graft (one) or deteriorating renal function (one) In both these patients the duration of history was >4 weeks.

This pilot study has demonstrated that ^{111}In-P256 imaging can identify sites of acute arterial thrombosis and provide additional information to arteriography, and may identify those patients most likely to benefit from thrombolysis

Epidemal growth factor receptor (EGFR) status: a clinically useful prognostic indicator in axillary node negative breast cancer

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The presence of axillary lymph node metastases is the most powerful prognostic indicator in breast cancer Not all surgeons, however, routinely sample the axillary lymph nodes and these data do not predict the likelihood of response to either systemic adjuvant therapy or to systemic therapy at relapse.

In a series of 221 patients with operable breast cancer, followed for up to 5 years after surgery, EGFR expression was associated with poor prognosis ($P<0\cdot001$, log rank) and was inversely related to oestrogen receptor (ER) status ($P<0\cdot0001$) In a multivariate analysis of survival data, EGFR status was the only significant prognostic variable in patients with negative and unsampled (clinically negative) axillary lymph nodes

Of 99 out of 221 patients with a documented recurrence, 72 had assessable responses to systemic endocrine therapy. EGFR expression was significantly associated with a lack of response ($P<0\cdot01$) and rapid disease progression ($P<0\cdot005$, log rank), and appeared to be more useful than ER status in predicting response to endocrine therapy.

In conclusion, EGFR status was a significant prognostic indicator in patients with clinically or histologically negative axillary lymph nodes, and predicted response to systemic endocrine therapy in patients with recurrent breast cancer with greater utility than ER status EGFR status may prove to be valuable in selecting node negative patients and those whose nodes have not been sampled for adjuvant systemic endocrine therapy.

Epidermal growth factor receptor (EGFR) in primary breast cancer

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EGFR measured by binding assay and immunohistochemistry has been claimed to be a powerful prognostic factor in breast cancer[1].

Ninety invasive breast cancers held in freeze-dried storage were stained by an indirect peroxidase method with a monoclonal antibody to EGFR The staining was graded by two observers and the results were correlated with a number of established tumour prognostic variables, together with disease-free interval (DFI) Actuarial methods were used in the determination of DFI The maximum follow-up was 36 months

Seventy-five tumours were EGFR negative and 13 were EGFR positive. Results showed that (a) there was a significant inverse correlation between EGFR staining and oestrogen receptor (ER) measured by the dextran-coated charcoal method, (b) there was no relationship of EGFR to histological grade; and (c) the combination of EGFR positivity and ER negativity predicts early recurrence

EGFR measured by immunocytochemistry in primary breast cancer is confirmed as a prognostic factor in the prediction of early recurrence. However, even in combination with ER, prediction is not as powerful as that attained by histological grade.

1. Sainsbury JRC, Farndon JR, Needham GK, Malcolm AJ, Harris AL. Epidermal growth factor receptor status as predictor of early recurrence and of death from breast cancer *Lancet* 1987, **i**. 1398–402

Prognostic value of immunoperoxidase staining with monoclonal antibodies NCRC-11 and 3E1.2 in breast cancer

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Monoclonal antibody (MoAb) NCRC-11 has been shown to identify an antigen which has prognostic significance in patients with breast cancer[1] However, other studies with this and other MoAbs have failed to show prognostic value.

The present study comprised 483 patients in a second centre with a minimum follow-up of 5 years. Paraffin blocks of primary tumour were stained with NCRC-11 and with a second MoAb, 3E1 2. Sections were examined by light microscopy and given a score on the scale 1–4

For any tumour the staining scores with both antibodies were similar, $r=0\cdot70$, $P<0\cdot001$.

Life-table analysis showed that both MoAbs related to survival NCRC-11, together with lymph node positivity, progesterone receptor status, size and age, was sustained as an independent variable in a Cox multivariate analysis ($\chi^2=5\cdot9$, $P<0\cdot02$)

3E1 2 related to survival only in lymph node negative patients ($\chi^2=10\cdot7$, $P<0\cdot001$).

NCRC-11 is confirmed in a separate series as a powerful prognostic factor in breast cancer.

1 Ellis IO, Hinton CP, MacNay J *et al* Immunocytochemical staining of breast carcinoma with the monoclonal antibody NCRC-11 a new prognostic indicator *Br Med J* 1985, **290**. 881–3

Tumour bed biopsy: a new prognostic indicator following conservative management of early breast cancer

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Breast cancer recurrence following lumpectomy and radiotherapy cannot be predicted in individual women. We have investigated the significance of tumour foci in bed biopsies taken at the time of lumpectomy in a consecutive series of 117 women with early breast cancer treated at one unit since 1986.

Following lumpectomy, residual tumour was found in 32 (27·4 per cent) of cases, in 17 as invasive and in 15 as *in situ* cancer. Management by breast irradiation was changed as a reult of bed biopsy findings in nine women who underwent mastectomy.

After 3·5 years 84·6 per cent of women with negative biopsies were alive without disease compared with 62·3 per cent with positive biopsies (life-table analysis). When other prognostic factors were considered, 56·3 per cent with nodel metastases were alive and disease-free compared with 94·4 per cent of node negative cases (χ^2 test, $P<0\cdot05$). When both node and bed biopsy positivity were considered, a group ($n=10$) was identified which fared particularly badly, only 35·5 per cent surviving disease-free compared with 95·7 per cent in the group ($n=62$) with neither risk factor (χ^2 test, $P<0\cdot01$). All groups were equivalent for age and oestrogen receptor status.

Bed biopsy status is an important risk factor in the assessment of the suitability of women for conservative management of early breast cancer.

Natural history and origin of the populations of breast cysts

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Two populations of breast cysts can be defined on the basis of electrolyte composition of cyst fluid (apocrine cysts, $Na^+:K^+<3$; flattened cysts, $Na^+.K^+\geqslant 3$) It has been reported that cyst type tends to remain constant in individual patients and that multiple cysts are more likely to be of apocrine type[1]. Recently these findings have been challenged and the view expressed that flattened cysts arise from apocrine cysts by increase in size or ageing[2].

In the present study we have analysed 1059 cysts aspirated from 420 patients over an 8-year period. Cyst type remained constant in 62 per cent of 237 patients with multiple cysts. The ratio of apocrine:flattened cysts (A:F) increased as the total number of cysts aspirated increased.

	No of cysts aspirated				
	1	2, 3	4, 5	6–10	7–10
Ratio A:F	1·18	2·30	3·15	4·03	12·40

Neither volume (studied in 100 patients) nor length of history (studied in 75 patients) correlated with composition.

In conclusion, cyst type remained constant in 62 per cent of patients and multiple cystic disease is usually apocrine cystic disease. Flattened macrocysts do not arise from apocrine macrocysts by expansion or ageing.

1. Dixon JM, Scott WN, Miller WR Natural history of cystic disease: importance of cyst type. *Br J Surg* 1985; **72**: 190–2
2. Ebbs SR, Bates T. Breast cyst type does not predict the natural history of cyst disease or breast cancer risk. *Br J Surg* 1988, **75**: 702–4.

Importance of routine mammography in the management of patients with small breast cancers

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It is not universal practice to perform mammography in all patients undergoing conservation therapy for breast cancer This study assesses whether routine mammography provides valuable information in the assessment of which small breast cancers are suitable for breast conservation.

Two hundred patients aged 70 years or less with a single palpable breast cancer measuring less than 4 cm staged T1 or T2, N0 or N1 and M0 were studied.

In 149 (74·5 per cent) mammography confirmed a localized malignant lesion, while in 32 (16·0 per cent) no suspicious lesion was identified. The remaining 19 patients had mammographic abnormalities not evident on clinical examination. Six had extensive areas of suspicious microcalcification associated with the carcinoma; six patients were considered mammographically to have more than a single focus of carcinoma; and seven patients had contralateral suspicious lesions. Subsequent histology showed all six areas of microcalcification to be associated with *in situ* malignancy and all six patients with more than a single mammograpic lesion were confirmed to have multifocal disease Five of the seven contralateral lesions were shown to be malignant.

In this study mammography indicated that 6·0 per cent of patients (those with microcalcification or multifocal disease) were unsuitable for breast conservation. A further 2·5 per cent of patients were found to have contralateral carcinomas. Routine mammography is essential in the management of patients with small breast cancers.

Peritoneal cytology for 'query appendicitis'

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Overall rates of diagnostic error for appendicectomy have been reported as 25 per cent and this figure can rise to 40 per cent in women of child-bearing age. We have evaluated the role of peritoneal cytology (PC) in discriminating which patients with right iliac fossa pain should undergo operation[1].

Fifty-one patients with acute right iliac fossa pain were classified into two groups according to a prior clinical decision· (I) definitely appendicitis and (II) 'query appendicitis' (including all women). Peritoneal aspirates, obtained via a fine catheter, were examined microscopically and the peritoneal neutrophil percentage (PNP) was counted. All patients in group I proceeded to appendicectomy and those in group II to laparoscopy, thus giving a final diagnosis in all.

All 16 patients in group I had appendicitis and the PNP was > 50 per cent in all. Of the 35 patients in group II, 18 required operation: PNP was > 50 per cent in 17 with appendicitis and fresh blood was aspirated in one patient with ectopic pregnancy. Seventeen patients in group II did not require operation the PNP was < 10 per cent in 15 and > 50 per cent in two, both patients with acute pelvic inflammatory disease (PID).

In this study PC has a sensitivity of 97 per cent and a specificity of 88 per cent. The benefit of PC is restricted to the 'uncertain group'. We suggest that PC should be applied to this group: if the result is positive then the patient should proceed to laparotomy unless PID is a clinical possibility in which case laparoscopy is required to avoid an unnecessary laparotomy.

1. Stewart RJ, et al Fine-catheter aspiration cytology of peritoneal cavity improves decision-making about difficult cases of acute abdominal pain *Lancet* 1986; **ii** 1414–15.

Strip testing of the peritoneal exudate reliably identifies intraperitoneal inflammation

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Cytological examination of peritoneal fluid obtained via a fine catheter is a sensitive technique for identifying patients with intraperitoneal inflammation, a preponderance of neutrophils possibly indicating the need for surgical exploration[1]. However, cytology may be time consuming and observer dependent. Chemical strip tests of the type used in routine urine testing detect leucocytes by an esterase reaction and might simplify the examination of peritoneal fluid for neutrophils. We have compared conventional cytology with strip testing of the same peritoneal fluid. Peritoneal aspirates were obtained just before laparotomy in 50 patients who were undergoing either elective abdominal surgery for non-inflammatory conditions or emergency laparotomy for intraperitoneal sepsis. Chemical testing was performed with Nephur-Test + Leuco (NTL, Boehringer Corporation, Lewes, UK) and Cytur-Test (CT) strips, for which positive criteria were > 75 and > 25 leucocytes/μl respectively. Conventional cytology was considered positive if the aspirate contained >50 per cent neutrophils. Results were as follows:

	NTL	CT	Cytology
Emergency surgery group (positive tests/n)	22/23	19/19	14/16
Elective surgery group (positive tests/n)	1/24	0/27	0/24
Sensitivity (%)	96	100	88
Specificity (%)	96	100	100

Strip testing is quicker and simpler method of assessing the peritoneal exudate for the presence of leucocytes and appears to be as specific and sensitive as standard cytological examination.

1. Stewart RJ et al. Fine-catheter aspiration cytology of peritoneal cavity improves decision-making about difficult cases of acute abdominal pain. *Lancet* 1986; **ii**: 1414–5.

Targeting of microdiscs in neutrophils to rabbit appendix abscess

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The ability to deliver drugs to a specific focus of infection has been a much sought-after goal. The main obstacle is the reticuloendothelial system (RES) In order to reduce RES uptake we investigated the possibility of 'hiding' microdiscs within neutrophils and delivery to an experimental appendix abscess

The abscess was created in 11 New Zealand white rabbits by luminal obstruction with a balloon catheter. In six animals 2×10^6 white blood cells (WBC) were separated from peripheral blood and incubated with 3 μm ^{76}arsenic-labelled silicon microdiscs. In a further five animals microdiscs were injected without prior incorporation into the white cells The animals were sacrificed 2 h later and radioactivity counts were determined from homogenized tissue of appendix and an equivalent length of normal jejunum

	Microdiscs in WBC ($n=6$)	Microdiscs alone ($n=5$)	P*
Ratio of radioactive counts, appendix:jejunum (c.p.m./g)	2·47	0·96	<0·001

* Mann–Whitney U test

These results demonstrate that intracellular microdiscs can be actively targeted to an area of sepsis, evading the RES, and could contribute to the local management of surgical sepsis.

Peritoneal fibrinolytic activity and adhesions

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A unifying hypothesis[1] states that peritoneal fibrinolytic activity is reduced in conditions that lead to adhesion formation. We have examined this hypothesis by measuring plasminogen activator activity (PAA), tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI) of human peritoneum.

Peritoneal biopsies were obtained operatively using a 6mm biopsy punch from normal ($n=10$) and inflamed ($n=7$) human peritoneum. The samples were homogenized, and assayed by fibrin plate lysis (functional assay) for PAA and by ELISA for both t-PA and PAI.

	Normal	Inflamed	P*
PAA (units/cm²)	12·0	0·0	0·001
t-PA (ng/ml)	1·03	1·02	n.s.
PAI (ng/ml)	0·0	8·8	0·001

* Mann–Whitney U test

These results demonstrate that functional fibrinolytic activity present in normal peritoneum is abolished in inflammation. The elaboration of PAI appears to be central to this change in functional activity. Modification of this response may ultimately be of benefit in prophylaxis of adhesion formation.

1. Raftery AT. Effect of peritoneal trauma on peritoneal fibrinolytic activity and intraperitoneal adhesion formation. *Eur Surg Res* 1981; **13**: 397–401.

Prospective randomized study of ingrowing toenail management

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A prospective, single-blind, randomized, parallel-group study compared total nail avulsion (group I), nail edge excision alone (group II) and nail edge excision with germinal matrix phenolization (group III). One hundred and sixty-three consecutive patients with ingrowing toenails in whom conservative treatment had failed and who had not had previous surgery were recruited. Bacteriological cultures of nail bed discharge were taken pre- and postoperatively Patients were assessed at 2 weeks and 1 year after surgery. Demographic data for the three groups were comparable. Preoperative infection did not predispose to postoperative sepsis. Although most wounds in the phenolized group (III) were moist at 2 weeks, only seven (12 per cent) were infected The incidence of recurrence was 73 per cent (group I), 73 per cent (group II) and 9 per cent (group III), respectively The incidence of recurrence (9 per cent) in the phenolized group (III) was significantly lower ($P<0·001$) than in the other two groups. These results are comparable to other series[1] However, assessment was independent in our study, and follow-up was prolonged. Nail edge excision with phenolization is a logical and effective treatment for ingrowing toenails. Non-ablative procedures should have no place in hospital practice, except where there is an absolute contraindication to the use of phenol.

1. Sykes PA. Ingrowing toenails: time for critical appraisal? *J R Coll Surg Edinb* 1986; **31**: 300–4.

Modulation of the neutrophil respiratory burst and alveolar capillary permeability in sepsis-induced acute respiratory distress syndrome by the non-steroidal anti-inflammatory drug, ibuprofen

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The effects of ibuprofen, a cyclo-oxygenase inhibitor, on phagocyte respiratory burst and parameters of alveolar capillary membrane permeability were studied in a porcine model of septic acute respiratory distress syndrome. Anaesthetized swine (20–25 kg) were intubated and mechanically ventilated ($FiO_2 = 0·5$). Control animals (C) received a sham infusion of 0·9 per cent NaCl, septic animals (Ps) received a 1 h infusion of live *Pseudomonas aeruginosa* (5×10^8 colony forming units ml^{-1} at 0·3 ml 20 kg^{-1} h^{-1}) and a treated group (I) received Ps plus ibuprofen (12·5 mg kg^{-1} at 0 and 120 min) Peripheral blood neutrophils (PMN) were isolated and bronchoalveolar lavage (BAL) was performed to study BAL protein (BAL-P) and alveolar neutrophil percentage (AN % – percentage total cell harvest) at 0 and 5 h. PMN superoxide ($O_2\cdot$) production was assessed as the maximum initial rate of superoxide dismutase inhibitable cytochrome C reduction (PMA stimulation)

	PMN $O_2\cdot$ (nmol min^{-1})		BAL-P (μg ml^{-1})		AN (%)	
Group	0 h	5 h	0 h	5 h	0 h	5 h
C ($n=6$)	1·05(0·2)	1·23(0·2)	171(17)	145(19)	3(1)	3(2)
Ps ($n=5$)	0·93(0·1)	8·05(0·7)*	170(17)	690(150)*	3(2)	25(8)*
I ($n=5$)	1·07(0·2)	4·13(0·8)	114(19)	143(23)	2(1)	5(1)

Values are mean (s.e.m.) $P<0·01$ Ps *versus* C and I, ANOVA

Ibuprofen attenuated PMN generation of $O_2\cdot$, indicating a down-regulation of oxidant generation, *in vivo*, following sepsis. Ibuprofen also prevented increased airways protein and neutrophil accumulation indicating protection of the alveolar epithelial membrane. This dual effect of ibuprofen may have important implications in the treatment of acute respiratory distress syndrome in forthcoming human trials.

Randomized trial of streptokinase and tissue plasminogen activator in peripheral arterial thrombolysis

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Fifty-five patients have been recruited into a randomized parallel-group comparison of three thrombolytic regimens. Eighteen patients received intra-arterial streptokinase (SK), 19 received intra-arterial tissue plasminogen activator (IA t-PA) and 18 patients received intravenous t-PA (IV t-PA). There were no significant differences in age, duration of history, length of occlusion or presence of neurosensory deficit between the groups.

Initially successful lysis was significantly greater with IA t-PA than with either SK ($P<0·04$) or IV t-PA ($P<0·003$). The duration of therapy varied from a median of 30 h with IA t-PA to 40 h with SK (not significant). The mean increase in ankle:brachial index following IA t-PA (0·59 (0·28)) was significantly higher ($P<0·001$) than for either SK (0·31 (0·33)) or IV t-PA (0·25 (0·31)). Limb salvage was achieved in 79 per cent (IA t-PA), 50 per cent (SK) and 44 per cent (IV t-PA).

Haemorrhagic complications occurred in five patients following SK administration (two major, three minor), and in 11 patients following IV t-PA administration (one cerebrovascular accident, three major, four minor). In contrast there were no periods of hypotension, no transfusions were required, and only one minor haemorrhage occurred following IA t-PA ($P<0·05$).

IA t-PA provides a more effective, safer fibrinolytic treatment than conventional therapy with SK. Systemic t-PA administration has not been as successful, with a significantly higher risk of haemorrhagic complications

Restriction fragment length polymorphisms in the region of the oestrogen receptor gene: a new prognostic indicator

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Oestrogen receptors are important markers of mammary tumour hormonal dependence and prognosis. The oestrogen receptor (ER) gene is a 'candidate gene' for mutation or abnormal transformation which may predispose to neoplasia. Cloning of the ER copy DNA (ERcDNA) has allowed comparison of the ER gene from breast cancer patients with that from normal subjects.

We have studied total genomic DNA prepared from tumour tissue of 81 patients with breast cancer and lymphocytes from 70 normal volunteers. The DNA was digested by seven different restriction endonucleases and restriction fragment length polymorphisms (RFLPs) identified by southern blot analysis using probes pOR_8 and pOR_{21} from the 5′ translated and 3′ untranslated regions of human ERcDNA respectively. Analysis of Msp1, Rsa1, Hae2 and Sau3a digests failed to demonstrate any consistent differences after hybridization and autoradiography. Digestion with $EcoR_1$, Taq_1 and Sac_1 revealed RFLPs specific to tumour patients (*Table 1*).

Table 1 *Summary of tumour-specific polymorphisms*

Restriction enzyme	Probe	Fragment size (kilobases)	Frequency of occurrence	
			Tumour	Control
$EcoR_1$	pOR_{21}	5·0	2/15	0/50
Taq_1	pOR_{21}	2·0	3/45	0/50
Sac_1	pOR_{21}	4·76	19/21	21/21

All seven patients showing these polymorphisms had advanced stage III disease at presentation and four demonstrated disease progression at a mean follow-up of 18 months.

We conclude that ER gene analysis not only provides further insight into the aetiology of breast cancer but may be of considerable prognostic significance.

Antirejection therapy in renal transplantation: OKT3 or methylprednisolone?

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The development of monoclonal antibodies against human lymphocytes has provided a new therapeutic alternative in the treatment of acute rejection.

In this study the success of antirejection therapy was evaluated in 65 cadaveric renal allografts immunosuppressed with cyclosporin. All first rejection episodes were treated with 0·5 g methylprednisolone (MP) given daily for 3 days (group A) Second rejection episodes were treated with either a further 3-day course of MP (group B) or a 10–14-day course of the monoclonal antibody OKT3 (group C)

Group	Rejection reversals*	Grafts surviving*	Peak creatinine† (μmol/l)	Creatinine at 6 months† (μmol/l)
A ($n=41$)	29 (71)	34 (83)	312 (116)	203 (78)
B ($n=14$)	9 (64)	12 (86)	320 (128)	230 (71)
C ($n=10$)	10 (100)	8 (80)	480 (174)	160 (42)
A *versus* B	n.s	n.s	n.s.	n.s.
A *versus* C	n.s	n.s.	$P=0·022$‡	n.s.
B *versus* C	$P=0·047$§	n.s	$P=0·036$‡	$P=0·024$‡

*Number (percentage), † mean (s.d.), n.s., not significant; ‡ Mann–Whitney *U* test; § Fisher's exact test

When treating second rejection episodes, a higher reversal rate was achieved with OKT3 therapy The most severe rejection episodes, as judged by peak creatinine, were found in the OKT3 group Despite this the creatinine at 6 months was lower in the OKT3 group than in either of the MP groups

In conclusion, treatment of second rejection episodes with OKT3 gives improved graft function at 6 months.

Tumour-derived suppressor factor impairs the autocrine function of lymphokine-activated killer cells

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Previous work suggests that the immunotherapy of malignant disease, either with recombinant cytokines or adoptive transfer of cytokine-activated lymphocytes, fails because of immunosuppressive factors produced by tumour cells[1] Cytokines normally bind to specific receptors on the lymphocyte surface and cause activation by inducing intracellular second messengers. These can be detected as inositol phosphates (IP) and cyclic AMP (cAMP).

We have measured the production of intracellular IP_2, IP_3 and cAMP in lymphocytes activated by the cytokines interleukin 2 (IL-2), interleukin 4 (IL-2) and prostaglandin I_2 (PGI_2), in the presence and absence of tumour-derived suppressor factor (TDSF).

TDSF did not influence the production of IP_2 or IP_3 signals. The PGI_2 induced cAMP signal was reduced by 90·6 per cent at peak of control response (30 s) and the integrated response was reduced by 65 per cent The AMP signal is implicated in the secretion of interferon γ (IFN-γ), which is vital for activation of lymphocyte cytotoxicity towards tumour cells[2] We measured the production of IFN-γ by activated lymphocytes and found it to be reduced by 70 per cent in the presence of 25 per cent TDSF.

We conclude that TDSF subverts the immune response by inhibiting the autocrine secretion of IFN-γ at the second messenger level. This knowledge may lead to the design of more effective immunotherapeutic protocols

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2. Giovarelli M, Santoni A, Jemma C *et al.* Obligatory role of IFN-γ in induction of lymphokine-activated and T-lymphocyte killer activity, but not boosting of natural cytotoxicity. *J Immunol* 1988, **141**: 2831–6.

Reduced tissue fibrinolysis in a model of hind limb venous hypertension

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Pericapillary fibrin deposition is found in association with venous ulceration[1]. Interstitial tissue fibrinolysis has been shown to be depressed in the legs of patients with healed venous ulcers or simple varicose veins who had proven venous valvular incompetence[2]. The aim of this study was to discover whether induced venous hypertension caused changes in tissue (skin) fibrinolysis.

Eight canine common femoral side-to-side arteriovenous fistulae were formed. Radiolabelled fibrin clots were produced by subcutaneous injection of ^{125}I-labelled fibrinogen and thrombin 8 weeks after fistula formation. The lysis rate was measured, and a clearance half-life was calculated[2]. Skin was taken from the midpoint of the affected and control hind limbs, snap frozen, homogenized, and assayed for tissue plasminogen activator (t-PA) with a sensitive bioimmunoassay.

	t-PA level (units/g)	Fibrin clearance ($t_{1/2}$)
Hypertensive limbs	594 (482–925)	6 (5–9)
Control limbs	849 (712–2044)	5 (4–6)

Values are median with range in parenthesis

Fibrin clearance was prolonged and the t-PA level was lower in the hypertensive limb in seven out of eight cases ($P<0{\cdot}05$ for both sets of data on the Wilcoxon test).

These results support the concept that venous hypertension causes a diminution in tissue fibrinolysis.

1 Browse NL, Burnand KG. The cause of venous ulceration *Lancet* 1982; **ii**: 243–5

2. Gajraj H, Browse NL. Calf pump failure and fibrinolysis *Br J Surg* 1989, **76**: 646

Ranolazine: a new drug with beneficial effects on quality of renal preservation

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Ranolazine (Syntex Pharmaceuticals, Maidenhead, UK) is a new drug with a novel mode of action as a metabolic modulator and membrane stabilizer. In this double-blind trial of 30 bilaterally nephrectomized pigs, the left kidney was autotransplanted after preservation for 24 h in phosphate buffered sucrose (PBS140). Ten pigs were randomized to each of three groups: A, placebo; B, intravenous ranolazine before nephrectomy and in PBS140 flush and storage; and C, intravenous ranolazine after transplantation. Renal function was studied by measurement of perioperative blood flow; postoperative urine output; serum and urine urea, creatinine and osmolarity; inulin, PAH and lithium clearances for 14 days. Decoding of the first 25 animals allows us to report the results in the *Table*.

	Group A ($n=9$)	Group B ($n=9$)	Group C ($n=6$)
Death in renal failure	2	1	3
Weight (kg)	31·1 (0·7)	31·9 (1·8)	32·6 (2·2)
Peak serum urea (mmol/l)	43·4 (6·0)	28·5 (3·4)	33·4 (3·8)
Peak serum creatinine (μmol/l)	1063 (140)	754 (93)	840 (62)
Time to creatinine <200 μmol/l (days)	10·2 (4·2)	6·4 (0·9)	8·7 (2·3)
Peak urine flow (ml/h)	226 (23)	215 (28)	208 (123)
GFR at day 7 (ml/min)	16·4 (6·1)	56·6 (17·8)*	11·0 (7·1)
Peak GFR (ml/min)	47·8 (12·2)	104·8 (23·3)†	45·0 (21·7)

Values are mean (s.e.m.), GFR, glomerular filtration rate; * $P<0{\cdot}05$, † $P<0{\cdot}05$ (Student's t test)

This detailed study shows that porcine kidneys preserved in PBS140 containing ranolazine achieved superior renal function within 1 week of transplantation, and this benefit remained significant at 2 weeks

Modulation of colon cancer fatty acids by dietary n-3 lipids results in tumour growth suppression

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Colorectal cancer is linked epidemiologically to a high saturated fat diet, perhaps by increasing the availability of arachidonic acid and its metabolites which are tumour promoting Paradoxically this also suggests the possibility of treatment by dietary manipulation In order to investigate this, 1×10^7 colo-320 tumour cells were injected subcutaneously into each of 30 nude mice receiving either a 20 per cent saturated fat diet or 20 per cent n-3 polyunsaturated fat (Maxepa®, Duncan, Flockhart and Company, Greenford, UK) diet over 4 weeks Tumour size was determined by *in vivo* cast modelling (volume) during growth and by weight following excision. Tumour lipids were extracted and analysed by advanced tube capillary gas chromatography (sensitivity in the pmol range).

Tumour growth (mean (s d)) was reduced by the n-3 diet at 3 weeks (0·14 (0·05) *versus* 0·09 (0·04) cm^3, $P<0{\cdot}02$) and 4 weeks (0·61 (0·38) *versus* 0·29 (0·16) cm^3, $P<0{\cdot}02$; 0·60 (0·34) *versus* 0·28 (0·16) g, $P<0{\cdot}02$). There was reduction of tumour arachidonate by the n-3 diet (0·72 (0·18) *versus* 0·44 (0·16) nmol/mg protein, $P<0{\cdot}02$) and enhanced n-3 fatty acids especially eicosapentanoate (trace *versus* 0·82 (0·13), $P<0{\cdot}005$), 22.5 n-3 (0·18 (0·18) *versus* 0·78 (0·24), $P<0{\cdot}005$) and docosahexanoate (0·15 (0·1) *versus* 0·73 (0·34), $P<0{\cdot}005$) The effects were particularly striking in the tumour phospholipid fraction (i.e. the major fraction of arachidonic acid metabolism) (two-tailed Mann–Whitney U test).

These original findings show that dietary n-3 fats not only reduce the arachidonate content of a growing tumour, but greatly enhance the content of docosahexanoate and eicosapentanoate which are potent inhibitors of enzymes producing tumour-promoting arachidonate metabolites. This dual mechanism may explain the striking tumour growth suppression by n-3 fats.

Increased arachidonic acid in experimental colorectal tumours

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The relationship between dietary fat and colorectal cancer is not fully understood. This study examines the effect of dietary fat on colonic tumour induction and membrane fatty acid composition in male Wistar rats.

Fifty rats each were fed on either diet A (5 per cent saturated fat) or B (20 per cent saturated fat). Colorectal tumours were induced by intraperitoneal injection of azoxymethane (AOM) ($n=40$) and control animals received saline ($n=10$). Between 6 and 26 weeks animals were killed at intervals for histology and lipid analysis. Membrane fatty acids in erythrocytes, adipose tissue, colonic mucosa and colorectal tumours were determined by gas liquid chromatography.

Animals fed on diet B developed more tumours (1·86 (0·43) per rat) than those fed on diet A (0·8 (0·28) per rat) (mean (s e m.), $P=0{\cdot}03$, Mann–Whitney U test). Lipid analysis demonstrated a markedly increased content of arachidonic acid in tumours compared with colonic mucosa (*Table*) Furthermore, dietary fatty acid composition was found to influence the profile of membrane fatty acids in colonic mucosa

	Palmitic acid	Stearic acid	Oleic acid	Linoleic acid	Arachidonic acid
Mucosa	24·7(5·7)	9·3(0·41)	40·4(1·0)	16·9(0·9)	4·2(0·4)
Tumour	22·9(0·6)	11·3(1·0)	38·4(1·2)	15·4(1·1)	11·7(1·5)*

Proportional values of fatty acid content (mean (s e.m.)); * $P=0{\cdot}0025$, Mann–Whitney U test

The modulation of colonic mucosal membrane fatty acid composition by dietary fatty acids may increase the susceptibility of the colon to carcinogen. Arachidonic acid, which is the precursor molecule for prostaglandins, is a possible promoter or co-carcinogen in colorectal cancer.

Recovery from pouchitis: the mechanism of adaptive ileal villus regrowth

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Reservoir ileitis (pouchitis) is associated with acute diarrhoea which usually responds to metronidazole. To determine whether the severe villus atrophy typical of pouchitis is due to reservoir bacterial overgrowth and whether the mechanism of villus regrowth following treatment involves increased cellular proliferation, we have measured the crypt cell production rate (stathmokinetically), villus configuration and faecal bacteriology in 30 patients: (1) pouchitis ($n=10$), (2) no pouchitis ($n=10$), (3) ileostomy controls ($n=10$). The 20 pouch patients had repeat studies following metronidazole therapy

The crypt cell production rate (CCPR) was significantly higher in the pouchitis group, 2·05 (1·1–2·8)* cells/crypt/h (CCH), than in either the no pouchitis group, 1·0 (0·8–1·8)* CCH, or ileostomy controls, 0·8 (0·35–1·2)* CCH, $H=8{\cdot}517$, $P<0{\cdot}01$**. There was a positive correlation with severity of villus atrophy ($\phi=0{\cdot}68$*** $P<0{\cdot}01$). Following metronidazole treatment CCPR decreased in the pouchitis group from 2·05 (1·1–2·8)* to 0·9 (0·35–1·05)*, $z=3{\cdot}1$, $P<0{\cdot}05$, and the villus atrophy index increased from 1·0 (0·73–1·25)* to 1·8 (1·6–2·04)*, $z=-3{\cdot}78$, $P<0{\cdot}05$, signifying villus regrowth. These changes did not occur in patients with no pouchitis. Aerobic bacterial counts did not differ between the groups. Anaerobic counts were similar between the pouchitis patients, 2×10^8 ($2{\cdot}5\times10^6$–$3{\cdot}8\times10^9$)* CFU/ml, and those with no pouchitis, 4×10^8 ($1{\cdot}25\times10^7$–$5{\cdot}75\times10^9$)* CFU/ml, $z=1{\cdot}2$, n.s., with the ileostomies having significantly fewer counts, 1×10^6 ($2{\cdot}5\times10^5$–1×10^8)* CFU/ml, $H=9{\cdot}793$, $P<0{\cdot}05$**.

This study suggests that bacterial overgrowth is unlikely to be a cause of pouchitis and that the mechanism of adaptive villus regeneration induced by metronidazole involves an increased CCPR

* Median (95 per cent CI), ** analysis of variance, *** Spearman's rank correlation.

Transfusion status and extent of disease as predictors of recurrence of Crohn's disease

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In order to identify factors of predictive value in assessing the risk of recurrence after resections for Crohn's disease we have analysed the results of right hemicolectomy for terminal ileal or ileocolic disease in 197 patients (105 female and 92 male, mean age 31·1 years, range 15–62 years) operated on between 1947 and 1987. Recurrent disease was diagnosed in 73 (37 per cent) patients, this diagnosis was made radiologically in 52 (71 per cent), histologically in 19 (26 per cent) and endoscopically in two (3 per cent). Of the 73 patients with recurrence 49 (67 per cent) have undergone further surgery at some time. The mean follow-up in the non-recurrent patients is 8 years (range <1–35). Despite its established immunomodulatory effect in renal transplantation and possible importance in cancer surgery, perioperative blood transfusion was not found to be significantly associated with recurrence which occurred in 37·6 per cent of the transfused patients and 36·5 per cent of the non-transfused patients. However, the length of involved bowel as measured by the pathologist was very closely and highly significantly related to the risk of recurrence with a correlation coefficient of 0·955 ($P<0{\cdot}001$)

Pouchitis following restorative proctocolectomy: an evaluation of ^{111}indium-labelled granulocytes for diagnosis

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Acute ileal reservoir inflammation (pouchitis) occurs in 5–45 per cent of patients, 80 per cent of whom improve with metronidazole. Diagnosis may be difficult since inflammation has a patchy distribution when assessed by endoscopy or biopsy. We have evaluated ^{111}indium-labelled granulocyte scanning and faecal granulocyte excretion for diagnosis in 27 patients at 24 (18–33) months* following restorative proctocolectomy. Pouchitis on clinical, histological and sigmoidoscopic criteria was present in ten patients. Seven had positive scans and all seven had increased faecal excretion (sensitivity 70 per cent). The remaining 17 patients without pouchitis had 14 negative scans and normal faecal excretion (specificity 82 per cent, positive predictive value (PPV) 66 per cent, negative predictive value (NPV) 94 per cent) In patients with pouchitis and positive scans 1 month of treatment with metronidazole was associated with a significant reduction in the scan activity from a grade of 2 (2–3)* to 1 (0–1)*, $z=2{\cdot}882$, $P<0{\cdot}05$, and of faecal excretion from 7·5 per cent (4–31 per cent)* to 1·35 per cent (0·4–10 per cent)*, $z=1{\cdot}922$, $P<0{\cdot}03$. Metronidazole treatment was associated with a significant reduction in 24 h defaecation frequency from 8 (7–9)* to 5 (4–6)*, $z=2{\cdot}781$, $P<0{\cdot}05$, in sigmoidoscopic grade from 2 (2–3)* to 1 (0–1)*, $z=2{\cdot}882$, $P<0{\cdot}05$, and in the histological score from 4 (3–6)* to 1 (0–2)*, $z=2{\cdot}63$, $P<0{\cdot}05$. No change in these parameters was observed in patients receiving treatment who had negative scans.

This study shows that ^{111}indium granulocyte scanning is a useful method of diagnosis in pouchitis, particularly when inflammation is patchy. It also identifies patients who are likely to improve with metronidazole therapy

* Median (95 per cent CI)

Continuous pouch-anal manometry after restorative proctocolectomy

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Simultaneous ambulatory anorectal manometry has shown the importance of the sampling reflex for discrimination of rectal contents We have used this technique to study patients after restorative proctocolectomy (RP). Our hypothesis was that this important sampling reflex would be retained when the entire anal canal had been preserved with end-to-end anastomosis (EEA), that is without mucosectomy, but lost in those who had undergone mucosectomy with endoanal anastomosis (EAA)

Pouch and anal canal pressures were measured using a 2 mm diameter microtransducer catheter containing two sensors 6 cm apart. Pressures were recorded for 3 h on a portable microprocessor for subsequent computer analysis. Thirteen controls and 31 patients, 14 with mucosectomy, were studied They were encouraged to continue normal activities during the recordings. Results are shown in the *Table*.

	Control	EEA	EAA
Number of patients	13	14	17
Spontaneous sphincter relaxation	13	13	2
Sampling episodes (median/h)	4	5	0
Recognition of sampling episodes (%)	47	40	30

Spontaneous sphincter relaxation and sampling episodes were significantly reduced after EAA ($P<0{\cdot}01$, Mann–Whitney U test) In contrast, EEA preserves normal discriminatory function of the anal canal, supporting our hypothesis

Changing incidence of human papillomavirus-associated anal cancer, using a new technique for DNA hybridization of fixed tissue

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An association between anal squamous cell carcinoma (SCC) and human papillomavirus (HPV) has been reported[1]. In this country the incidence of benign genital papillomavirus infection has increased markedly over the last 20 years. We have examined a series of anal cancers collected over a 40-year period to look for changes in the incidence of HPV DNA in these tumours.

Existing methods for DNA hybridization of fixed tissue are insensitive and require large amounts of tissue. To overcome this problem we have adapted a technique of DNA preparation from whole cells[2] to examine fixed tissue by DNA hybridization. The age of the tissue specimen did not influence the signal obtained by this technique. This technique has been used to examine 200 tissue specimens from anal SCC.

There has been a threefold increase in the proportion of HPV related anal SCC in the last 10 years when compared with the previous 30 years ($\chi^2=15·6$, $P<0·001$). This parallels the rise in the incidence of HPV infections in the UK and supports the hypothesis that HPV may be an aetiological factor in anal cancer.

The new technique described for the DNA blotting of fixed tissues could be used to screen libraries of tissue for oncogenes in numerous applications.

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Is the gastrocolic reflex absent in diverticular disease?

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Ingestion of food normally stimulates colonic motility Patients with diverticular disease (DD) have symptoms after food, perhaps resulting from an anomalous prandial response. We have developed a novel aerial/computerized analysis system for use with free radiotelemetry pressure capsules. The left colonic motility index (MI), percentage activity, number of peaks >5 mmHg/h and number of peaks >50 mmHg/h were calculated for 1 h before and after meals in 21 patients with diverticular disease (seven mild, eight moderate, six severe disease) and six controls.

The preprandial motility index was 317 (114) in control subjects, increasing to 407 (133) after food. The corresponding values for patients with diverticular disease are shown in the *Table*.

	Mild DD	Moderate DD	Severe DD
Preprandial MI	247 (53)*	516 (114)**	1025 (169)**
Postprandial MI	520 (111)*	658 (132)**	1024 (93)**

* $P<0·05$, ** $P=$ not significant

The number of peaks >50 mmHg/h also increased with severity of DD (4·4(3) mild, 2·4(1) moderate, 15·5(4) severe), $P<0·05$. The corresponding postprandial values were 6·9(4), 7·8(5), 16·5(6).

These data suggest that the gastrocolic reflex is preserved in mild diverticular disease, but is absent in moderate/severe disease.

Portable non-invasive surface electromyography in the assessment of anal physiology: a comparative study

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Surface electromyography is sometimes considered a non-specific method for assessment of anal sphincter function. However, needle EMG is a painful examination and may therefore give spurious data. Anal manometry is the most common method to study anal functional disorders. We have carried out a prospective study to compare these two methods in order to determine the potential role of surface EMG in the assessment of anal physiology.

Using a specially designed portable unit, intra-anal integrated surface EMG and anal manometry were performed in 44 patients with various anorectal disorders at rest and during maximal voluntary sphincter contraction. Mean values of EMG activity were 37·9 μV (0–150, s.d. 35·4) and 114.9 μV (10–324, s.d. 78·4) and corresponding anal pressures were 93·1 cmH$_2$O (16–160, s.d. 38·9) and 212·8 cmH$_2$O (24–600, s.d. 123·7) at rest and at squeeze, respectively A significant correlation was found between results with both methods at rest ($P<0·001$, $r=0·521$) and squeeze ($P<0·001$, $r=0·791$) (least squares) When correlation between rest and squeezing activity in each isolated method was assessed, a higher correlation coefficient was found with the EMG ($P<0·001$, $r=0·847$) than with anal manometry ($P<0·001$, $r=0·675$).

These results suggest that intra-anal integrated EMG is a useful non-invasive portable method of assessing anal function which is superior to conventional manometry.

EMG biofeedback as a domiciliary treatment of anismus

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Anismus (spastic pelvic floor syndrome) is the inappropriate contraction of the pelvic floor while straining at stool and causes intractable constipation. The non-relaxation of the pelvic floor can be detected using an anal plug surface EMG electrode An electromyographically derived anismus index first compared the EMG activity during defaecation straining with the EMG activity during voluntary squeezing Biofeedback using visual display of the EMG signal was then used as a retraining exercise in 15 subjects (12 women and three men with a mean (s.d.) age of 45 (17) years) with constipation due to anismus. The anismus index pretreatment was 69·5 (28·7) (range from 43 to 160). The subjects were taught biofeedback suppression of the non-relaxing pelvic floor signal in hospital and had twice daily sessions using portable domiciliary biofeedback equipment for 2–4 weeks, the duration of treatment depending on their subjective responses (defaecation time, defaecation difficulty) measured on an analogue scale. The anismus index after biofeedback was 13·7 (16) (range from −25 to 35·7), $P<0·01$ All subjects had subjective improvement in defaecation times and in analogue scores for defaecation difficulty

A new method of limb blood flow measurement applied to diagnostic problems in vascular surgery: is it of value?

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In a patient with suspected claudication the history, signs, and ankle/brachial systolic pressure (Doppler) ratios may be inconsistent, making the diagnosis unclear We have developed a new method of limb blood flow measurement[1]. Normal flow is 11·3–21·6 ml/100 ml of tissue/min and flow to limbs with claudication is 1·8–8·25 ml/100 ml, does this technique help to manage such patients? Twenty-four patients presented as diagnostic problems. Eleven had a convincing history but six of these had palpable pedal pulses, the other five had normal Doppler ratios. Of 13 with a poor history six had absent pulses, and of the other seven with palpable pulses, two had abnormal and five had normal Doppler ratios

n	3	2
Limb blood flow	>8 ml/100 ml/min	<8 ml/100 ml/min
Diagnosis	Osteoarthritis of spine (2) or knee (1)	SFA occlusion (2)

All 24 patients have had blood flow to both legs measured. Twelve had reduced flows consistent with claudication (<8 ml/100 ml of tissue/min) Eight of these have undergone arteriography which demonstrated significant vascular disease, three await arteriography and one had surgery to rheumatoid toes deferred. Of 12 with normal flows three had normal arteriograms, the other nine have been found to have significant orthopaedic problems affecting spine, hips or knees In every case the history, signs or Doppler ratios were potentially misleading but all cases of significant arterial disease were detected by the new technique. It is cheap, readily available and effectively selected cases for referral or arteriography.

1. Parkin A, Robinson PJ, Wiggins PA *et al* The measurement of limb blood flow using technetium labelled red blood cells *Br J Radiol* 1986, 59: 493–7.

Platelet adhesion to human amnion, Dacron and PTFE assessed in vitro

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Successful clinical application of endothelial cell seeding of arterial prostheses to reduce thrombogenicity may be prevented by lack of suitable autogenous vein from which to harvest cells, variability in cell yields and rejection of cells obtained from cadaveric donors. Human amnion cells are readily available, do not express major histocompatibility antigens and survive after allotransplantation We have assessed the thrombogenicity of human amnion cells by estimation of labelled platelet adherence *in vitro*.

Segments of amnion from elective Caesarean sections, Dacron® (Du Pont) and polytetrafluorethylene (PTFE) were maintained in tissue culture for up to 23 days. Human platelets labelled with ^{111}indium oxine were exposed to the surface of each material for 40 min and removed by gentle washing Thrombogenicity was estimated as the ratio of the radioactivity remaining on the surface of each material after washing to the radioactivity of the initial platelet inoculum expressed as a percentage. Results are given in the *Table*.

	Before culture	After 23 days' culture
Amnion cells	7·0 (2·9)	8·0 (1·6)
Amnion reversed membrane	28·0 (4·9)	36·0 (11·6)
Dacron	67·0 (3·0)	42·0 (16·9)
PTFE	21·6 (3·3)	11·3 (1·2)

Values are mean(s.d.)

These data suggest that amnion cells have low thrombogenic potential and further investigation of their use in seeding arterial prostheses is warranted.

Can we select patients suitable for lumbar sympathectomy?

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Since not all patients respond favourably to lumbar sympathectomy a predictive test would assist in the management of the critically ischaemic limb. Duplex ultrasound volume flowmetry offers a precise non-invasive method for evaluating blood flow changes to the lower limb. Initially, the change in mean common femoral artery flow after postural change was studied in three groups of patients: normals ($n=12$), claudicants ($n=7$), and patients with rest pain ($n=9$) The mean (s.d.) change in blood flow was −78(116), −112(123), and 131(89) ml/min. Patients with rest pain showed a highly significant increase in common femoral artery flow ($P<0{\cdot}0001$, compared to normals). Claudicants responded significantly differently to normals ($P<0{\cdot}03$).

Eight patients were studied before and after lumbar sympathectomy. Patients with an initial high vasomotor tone exhibited a fall in flow with dependency (normal-type response), and showed a clinical improvement after sympathectomy, which was manifested by a lowered vasomotor tone Patients with an initial low vasomotor tone exhibited a poor symptomatic response to sympathectomy.

In conclusion, normal or mildly ischaemic limbs respond to dependency by a fall in axial artery limb blood flow. In contrast, patients with critical ischaemia and rest pain often show a rise in limb flow after dependency, as did those who underwent sympathectomy. Patients who exhibited a negative orthostatic flow response respond successfully to sympathectomy.

Outflow vascular resistance and early graft occlusion in the lower limb

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The 'run-off' of arterial bypass grafts may be assessed in terms of vascular resistance (VR). VR has been measured intraoperatively in the outflow artery of femoropopliteal and femorodistal grafts to establish its relationship to graft patency 10 days after surgery.

VR before and after intra-arterial papaverine injection was derived from the relationship between pressure and flow in the popliteal (36), tibial (eight) or peroneal (two) artery while the patient's own blood was infused into it at 74 ml/min. Graft patency or occlusion was determined by ankle pressure measurement, arteriography or re-exploration.

The VR of nine grafts which thrombosed was 1155(346) peripheral resistance units (mPRU), expressed as mean (s.d.), significantly greater than that of 37 patent grafts, 880(328) mPRU ($P=0{\cdot}02$). After papaverine, VR was 844(384) mPRU in thrombosed and 506(217) mPRU in patent grafts ($P=0{\cdot}005$). The VR value which indicated the outcome of bypass grafting most efficiently was 800 mPRU after papaverine This was 87 per cent accurate and had a sensitivity of 67 per cent, a specificity of 92 per cent and a predictive value of 67 per cent for graft thrombosis.

Early graft thrombosis is associated with a high outflow VR. A discriminative value has been defined which has high specificity for early graft thrombosis

Accidental injury causes prolonged suppression of the baroreflex in man

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Injury causes profound systemic effects and animal studies have shown that these may include an alteration of baroreflex function[1]. The baroreflex controls blood pressure and heart rate, thus playing a crucial role in acute cardiovascular homoeostasis.

Baroreflex function[2] was studied sequentially in 21 stable, moderately injured patients (injury severity score 9–17) and in 22 controls. Control baroreflex sensitivity was 3·70 (0·09–15·46) ms mmHg^{-1}, median (range). Compared with controls, marked baroreflex suppression was demonstrated within 4 h of injury (1·13 (−0·6–6·78) ms mmHg^{-1}, $P<0{\cdot}05$ using the Wilcoxon rank sum test), at 3 days after injury (1·36 (−0·1–2·77) ms mmHg^{-1}, $P<0{\cdot}001$ using the Wilcoxon rank sum test) and even 2 weeks after injury (2·57 (−0·08–6·52) ms mmHg^{-1}, $P<0{\cdot}05$ using the Wilcoxon rank sum test). Paired testing showed that partial recovery of baroreflex function occurred between 3 and 14 days after injury ($P<0{\cdot}01$ using the Wilcoxon signed rank test) Five months after injury, injured patients were indistinguishable from controls

Following injury, resting heart rate and blood pressure were elevated and sinus arrhythmia was reduced, with a time course similar to that of baroreflex suppression.

The arterial baroreflex is suppressed within 4 h of injury and remains so for 2 weeks. During this time the normal relationship between heart rate and blood pressure is lost. These changes in this important cardiovascular homeostatic reflex have clinical implications

1 Redfern WS, Little RA, Stoner HB, Marshall HW. Effect of limb ischaemia on blood pressure and the blood pressure heart rate reflex in the rat. *Q J Exp Physiol* 1984, **69**: 763–79.

2 Eckberg DL, Cavanaugh MS, Mark AL, Abboud FM. A simplified neck suction device for activation of carotid baroreceptors *J Lab Clin Med* 1975, **85**: 167–73

Reduced immune, haemostatic and cardiac function and increased postoperative stress-response may mediate increased postoperative morbidity in asymptomatic alcoholics

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Postoperative morbidity in alcoholics is increased[1,2]. To investigate possible mechanisms 14 asymptomatic alcoholics (≥60 g alcohol/day) undergoing elective colorectal resection were matched (sex, nutrition, age, weight, cardiovascular and pulmonary disease, diagnosis and surgery) to 14 controls (<25 g alcohol/day) in a prospective study. The following results were obtained (mean (s.e.m.), *$P<0{\cdot}05$, **$P<0{\cdot}01$, Mann–Whitney U test)

The preoperatively prolonged bleeding time in the alcohol group (AG), 3·4(0·3) min compared to the controls (CG) 2·1(0·2)**, continued on days 1 and 7 after surgery, 3·1(0·3) *versus* 1·9(0·3)**

Preoperatively, the ejection fraction (cardioscintigraphy) was reduced in the AG, 56(2) per cent compared to 69(2)**

Preoperatively, the AG had reduced delayed hypersensitivity (skin test response 56(1) mm^2 *versus* 110(19)**) and NK cell activity (18(4) per cent *versus* 46(4)** The postoperative day 1 suppression of NK cell activity was most pronounced in the AG, 7(1) per cent *versus* 29(7)** (day 1) and 14(3) per cent *versus* 27(6)* (day 7)

The AG's stress-response (cortisol) was higher 24 h postoperatively compared to the CG*.

Sixty-four per cent of the AG had postoperative complications (bleeding, cardiopulmonary, infectious) compared to 14 per cent in the CG** (χ^2 test).

Our results suggest that increased postoperative morbidity in alcoholics may be due to decreased haemostatic function, subclinical cardiac insufficiency, pre- and postoperative immunodepression and increased surgical stress-response.

1. Tonnesen H, Schutten BT, Jorgensen BB Influence of alcohol on morbidity after colonic surgery. *Dis Colon Rectum* 1987, **30**. 540–51

2. Tonnesen H, Schutten BT, Tollund L, Hasselqvist, P, Klintorp S Influence of alcoholism on morbidity after transurethral prostatectomy *Scand J Urol Nephrol* 1988; **22**· 175–7.

Reversal of supersensitivity in intimal hyperplastic rabbit aorta exposed to hypercholesterolaemia

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Vascular endothelial denudation results in intimal hyperplasia which is associated with increased sensitivity and increased maximal contraction in rabbit aorta in response to noradrenaline. The aim of this study was to characterize the effect of hypercholesterolaemia on contractility following endothelial denudation. Rabbit abdominal aorta was denuded using a balloon catheter ($n=14$) and significant intimal hyperplasia developed by 2 weeks. The rabbits were then fed an atherogenic diet containing 2 per cent cholesterol and were killed 1, 4 and 8 weeks thereafter. Isometric contraction in strips of denuded and non-traumatized (control) aorta was measured in an organ bath in response to cumulative doses of noradrenaline or histamine. Dose–response curves were constructed and compared at the 50 per cent maximal contraction level (EC_{50}). Results are given in the *Table*

Cholesterol	Control (EC_{50})	Denuded aorta (EC_{50})
1 week, $n=5$	6·80 ($1{\cdot}82\times10^{-6}$)	1·60 ($1{\cdot}46\times10^{-7}$) $P<0{\cdot}01$
4 weeks, $n=5$	6·67 ($1{\cdot}81\times10^{-6}$)	0·90 ($0{\cdot}50\times10^{-6}$) $P<0{\cdot}02$
8 weeks, $n=4$	5·27 ($2{\cdot}34\times10^{-6}$)	1·23 ($0{\cdot}89\times10^{-5}$) n s.

Molar concentration of noradrenaline, mean (s e.m.), Student's *t* test

These results confirm the previously demonstrated supersensitivity in intimal hyperplastic rabbit aorta to noradrenaline There was an increase to 171·4(23·7) per cent, mean (s.e.m.), in maximal contraction in atherosclerotic vessels in response to histamine. These data demonstrate that the increased contractile response to noradrenaline is reversed with the development of atherosclerosis and that it is replaced by increased histamine contractility.

Pulmonary platelet sequestration during major surgery

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Pulmonary dysfunction frequently occurs following major surgery and may be related to platelet microembolization. The influence of prostaglandin E_1 (PGE_1), a potent inhibitor of platelet activation, which improves perioperative pulmonary haemodynamics[1] was studied in 24 pigs during experimental surgery.

Autologous ^{111}indium-labelled platelets were injected 24 h prior to standardized surgery. *In vivo* ^{111}In-labelled platelet uptake in both lungs was measured with a highly collimated sodium iodide probe and ratemeter and expressed as a ratio to the reference area (head). Serial platelet count and pulmonary function were also recorded.

Pulmonary platelet uptake in controls rose from a mean of 3·68(1·02) at the start of surgery to 5·95(0·84) during surgery and 7·64(2·8) on the third postoperative day, and from 3·53(0·68) to 5·17(1·06) and 5·56(0·97) on PGE_1, a significantly greater rise ($P<0{\cdot}01$ Mann–Whitney *U* test) in controls The fall in platelet count was reduced from 163×10^9/l to only 72×10^9/l on PGE_1 ($P<0{\cdot}02$).

Alveolar–arterial oxygen difference (AaD_{O2}), an index of injury to the alveolar–capillary membrane, showed a very similar pattern to pulmonary platelet uptake rising to 27·35(3·63) mmHg in controls, compared with only 14·86(1·39) mmHg on PGE_1 ($P<0{\cdot}02$).

PGE_1 inhibited platelet consumption and the subsequent pulmonary sequestration of ^{111}In-labelled platelets which correlated with an improvement in postoperative pulmonary function

1 Hocken DB, Galvin DAJ, McCollum CN. The influence of prostaglandin E_1 on pulmonary and systemic haemodynamics during aortic surgery. *Eur J Vasc Surg* 1989; 3: 1–6.

Comparative study of 24 h ambulatory oesophageal pH in patients with erosive oesophagitis treated by cimetidine and omeprazole

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The effect of treatment of erosive oesophagitis by cimetidine (CIM) and omeprazole (OM) has been studied by 24 hour ambulatory oesophageal pH (24 h pH). Eighteen patients with endoscopic erosive oesophagitis were randomly allocated to receive 8 weeks of treatment, CIM 400 mg q.d.s. or OM 40 mg o.d. Ambulatory 24 h pH measurements were undertaken before and after 29 days of therapy Results of distal oesophageal acid exposure (<pH 4) are shown in the *Table* Endoscopic healing occurred in five CIM and six OM patients. Median total percentage <pH 4 were 5·9 (2·4–16·4) and 0·05 (0–0·1), respectively ($P=0{\cdot}0001$). Median percentage time <pH 4 in four CIM and three OM patients without endoscopic healing was 16·6 (7·5–36) and 10 (1·1–23), respectively. Before treatment reflux episodes/24 h were 35 (32–81) for CIM and 20 (9–65) for OM (P=n.s.). At day 29 these were 30 (4–61) CIM and 1·0–38 OM ($P=0{\cdot}001$). Before treatment the longest reflux episode (min) was 6 (2–40) CIM and 8 (1–58) OM, at day 29 these were 16 (0–33) CIM and 0 (0–10) OM ($P=0{\cdot}100$).

OM is more effective than CIM in reducing all parameters of gastro-oesophageal acid reflux.

Median percentage time for oesophagus <pH 4 (* $P=0{\cdot}0001$)

		Day time		Night time		Total	
	n	Day 0	Day 29	Day 0	Day 29	Day 0	Day 29
Cimetidine	9	10·48	10·25	7·66	11·56	9·51	10·78
Omeprazole	9	11·25	0·74*	11·31	7·10	11·43	3·37

Role of surgery in preventing reflux and complications in Barrett's metaplasia

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The presence of Barrett's metaplasia is a controversial indication for antireflux surgery[1] We comared the results of surgery and medical therapy in two groups of 20 patients with histologically proven Barrett's mucosa presenting during the 10 years from 1979, with mean follow-up of 3·4 years. Initial lower oesophageal sphincter pressures (LOSP) and pH profiles were comparable in both groups. The results are shown in the *Table*

	Surgical treatment ($n=20$)		Medical treatment ($n=20$)	
	Preoperative	Postoperative	Prereflux	Postreflux
Percentage time pH<4 median (range)	31·9(5·7–77)	0·5(0–41)	22·2(5·1–73·9)	13·6(0·3–79)
	$P<0{\cdot}01$		P=n s	
LOSP (mmHg) mean (s.e m)	10·04(0·8)	16·2(1·9)	11·5(2·02)	14·7(4·3)
	$P<0{\cdot}05$		P=n s	
Stricture/ ulceration	10	0	12	5
		$P<0{\cdot}05$		

Dysplasia regressed in four patients and progressed in one after surgery, while none regressed but four progressed after medical therapy Surgery provided better control of reflux, improved sphincter tone, reduced complications and resulted in improved grade of dysplasia.

1. Iascone C, DeMeester TR, Little AG, Skinner DB Barrett's oesophagus: Functional assessment, proposed pathogenesis, and surgical therapy *Arch Surg* 1983, **118**: 543–9.

Non-invasive detection of the gastric migrating motor complex by surface vibration analysis

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The migrating motor complex (MMC) is the key to gastrointestinal motility disorders, but conventional methods which address this parameter are invasive

In this study, a new computerized non-invasive test called surface vibration analysis (SVA) was evaluated against conventional manometry, for detection of the MMC in ten volunteers. Synchronous studies were carried out at 4 h intervals, first in the fasting phase, then again after acaloric liquid (350 ml isotonic lactulose) in all subjects.

In the fasting phase, SVA detected the gastric MMC in 7/10 volunteers, with a response which was proportional to intragastric pressure change. After liquid, fasting motility patterns persisted in eight volunteers and SVA detected the gastric MMC in all. Liquid enhanced the SVA response to the MMC, but had no effect on intragastric pressure ($\bar{x}$ (s.e.m.) = 40·64 (3·17) mmHg before; 39·3 (3·54) mmHg after liquid). SVA did not detect small bowel MMCs, which had low contractile pressures ($\bar{x}$ (s.e.m.) = 17·6 (3·5) mmHg).

SVA is a non-invasive test which can detect the gastric MMC. Two factors which determine the SVA response have been identified, i.e. contractile amplitude and intraluminal content.

Intestinal cytokinetics during the induction of chronic duodenal ulcer

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Chronic duodenal ulcer can be induced in mice as an indirect effect of lower mediastinal irradiation, the resulting ulcers closely resembling those seen in man. Using a stathmokinetic technique we have studied crypt cell production rate (CCPR) in 72 female CFLP mice weighing 25–40 g randomly allocated to three groups. Controls were anaesthetized only.

Irradiated animals received a single dose of 18 Gy 250 kV X rays to either the upper mediastinum (which never causes ulceration, irradiated control) or to the lower mediastinum (which induces ulcers in 45 per cent in 7 days, ulcer group). Studies were performed at days 3 and 7 postirradiation. Animals were killed at intervals from 30 to 180 min after vincristine (1 mg/kg IP) and the duodenum and small bowel were immediately removed and fixed before counting. The number of cells arrested in metaphase in 20 well oriented crypts per sample were plotted against time to give CCPR in cells/crypt/h (mean(s.e.m.)).

		Duodenum	Ileum
Day 3	Control	7·5 (2·85)	14·34 (2·7)
	Irradiated control	12·72 (3·42)	18·48 (2·0)
	Ulcer group	26·52* (2·52)	25·0 (4·7)
Day 7	Control	9·9 (3·42)	6·84 (1·56)
	Irradiated control	6·96 (2·64)	8·7 (2·7)
	Ulcer group	5·52 (2·58)	5·52 (1·56)

* $P < 0·01$

Duodenal CCPR trebled during ulcer induction but returned to normal by the time ulceration occurred. Cellular changes associated with ulceration may thus be demonstrable only in the induction phase rather than in the established ulcer. Further studies during this period may be central in understanding the mechanisms of chronicity in duodenal ulcer.

Non ulcer dyspepsia: a hypomotility disorder?

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Non ulcer dyspepsia (NUD) is a common gastroenterological diagnosis with obscure aetiology. In this prospective study, 40 symptomatic patients were diagnosed as NUD, after exclusion of peptic ulcer, gallstones and oesophageal reflux by endoscopy, ultrasound and 24 h pH monitoring, respectively. Gastric and small bowel function were investigated by measurement of six objective parameters in all patients: gastric emptying (GE), oral to caecal transit time (OCTT), antral campylobacter (CpB), small bowel bacterial overgrowth (SBBO), peak acid output (PAO), and enterogastric bile reflux (EGBR). All tests were validated in 20 healthy controls and abnormalities were defined as more than two standard deviations outwith the mean.

	GE (Delay)	OCTT (Delay)	CpB (+)	SBBO (+)	PAO (High)	EGBR (+)
Number of patients	23	11	16	8	2	1
Percentage of total (%)	58	28	40	20	5	2

In total 29/40 patients had hypomotility, with delayed GE and/or prolonged OCTT. All cases of bacterial overgrowth were associated with hypomotility.

In conclusion, hypomotility is common in NUD, is often accompanied by bacterial overgrowth, and may be implicated in aetiology

Human gastric tissue oxygenation and the effect of truncal vagotomy

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Non-uniform distribution of blood flow in the stomach has been demonstrated in previous studies and relative ischaemia has been implicated in the pathogenesis of peptic ulceration. In addition, vagotomy has been shown to decrease gastric blood flow. This study uses preoperative tissue oximetry to evaluate tissue oxygenation in the human stomach, of which little was previously known, and examines the effect of truncal vagotomy.

Using a Clark polarographic oxygen electrode with a linear response to oxygen ($r = 0·998$, $P < 0·001$), detailed 'mapping' of tissue oxygen tension levels (P_{tO_2}) on the anterior surface of the stomach was carried out in five patients. Although no significant difference in mean P_{tO_2} was detectable between greater and lesser curvatures of the stomach at any level, there was a significant difference in mean P_{tO_2} levels between the body and antrum (Mann–Whitney U test, $P < 0·01$).

The effect of truncal vagotomy on gastrointestinal P_{tO_2} was evaluated in six patients undergoing this procedure for duodenal ulceration. Mean postvagotomy stomach P_{tO_2} levels (46 (12) mmHg) were significantly lower (Wilcoxon test, $P < 0·001$) than prevagotomy levels (59 (14) mmHg).

This work provides the first objective evidence of relatively diminished tissue oxygenation in the ulcer bearing area of the stomach and confirms blood flow studies of the effects of vagotomy

Proximal highly selective vagotomy: an operation for type I gastric ulcer when fibrosis limits dissection of distal lesser curve

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Compared with Billroth I PG, highly selective vagotomy with ulcer excision (HSVE) was shown in the Sheffield trial to yield much better functional results in gastric ulcer (GU) patients, while recurrence rates were similar[1]. However, fibrosis along the lesser curve can render the procedure difficult to perform. Our hypothesis, based on the work of Oi[2], was that a vagotomy proximal to the ulcer might prove sufficient

Of 109 GU patients, 24 were treated by proximal HSVE and 85 by HSVE between 1970 and 1988. Median PAO^{Pg} was 15·3 mmol/h (upper quartile 18·6, lower quartile 10·35, $n = 13$) and 21·3 (UQ 27·9, LQ 15·12, $n = 47$) respectively before operation, and median reductions 1 week after operation, 79 per cent and 65 per cent, respectively. None of the insulin tests were positive after proximal HSVE three (7 per cent) were positive after HSVE. Recurrent ulceration developed in ten patients (12·9 per cent by life table analysis): two after proximal HSVE and eight after HSVE (n.s.): 84 per cent of patients were in Visick grades I + II after proximal HSVE and 82 per cent after HSVE (n.s.)

When fibrosis along the lesser curve limits dissection, vagotomy round the oesophagus and down the lesser curve as far as the ulcer denervates the parietal cells efficiently and yields good clinical results

1. Reid DA, Duthie HL, Bransom CJ, Johnson AG Late follow up of highly selective vagotomy with excision of the ulcer compared with Billroth I gastrectomy for treatment of benign gastric ulcer. *Br J Surg* 1982; **69** 605–7
2. Oi M, Oshida K, Sugimara S. The location of gastric ulcer. *Gastroenterology* 1959; **36**· 45–6

Vagotomy and ranitidine prevent the postprandial reduction in urine acid output

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Changes in urine acidity after a meal correlate inversely with gastric secretory capacity[1]. We investigated this response in patients after vagotomy and in normal volunteers.

In 16 volunteers, gastric peak acid output (PAO) after sham feeding (SF) was median 13 mmol/h, range 7·6 to 17. Sixteen patients had complete vagotomy (PAO to SF <7 mmol/h), and three with recurrent ulcer had an incomplete vagotomy (PAO >7 mmol/h).

Urine acid output in volunteers fell in the 2 h after a meal from basal values by a median −2·2 mmol/h (range −0·4 to −3·1). In seven volunteers given ranitidine 150 mg every 12 h (three doses) before the meal, the change in urine acid output was abolished (median +1·1 mmol/h, range +0·6 to 2·9). Complete vagotomy also abolished the normal postprandial response (median +1·3 mmol/h, range +6·7 to −0·3). In contrast, patients with incomplete vagotomy showed a postprandial fall in urine acid output (range −0·9 to −1·8 mmol/h).

This study shows that changes in urine acid output after food can separate normal volunteers from those given ranitidine and from patients with complete vagotomy. Incomplete vagotomy can be detected by failure to inhibit the normal reduction in urinary acid output.

1. Johnson CD, Harris P, Wastell C. An indirect tubeless test for gastric function. *Gut* 1988; **29**: A1452.

Does gallstone clearance require both extracorporeal shock wave lithotripsy and chemical dissolution? A randomized study

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Following extracorporeal shock wave lithotripsy (ESWL), it is not known whether fragments can be cleared from the gallbladder without the use of oral dissolution therapy (DT). To prospectively assess the efficacy of ESWL and DT, used alone or in combination, we randomized 31 patients to one of three treatment groups: ESWL alone, DT alone or ESWL and DT. All patients had symptomatic gallstones and functioning gallbladders, and the stone profiles were comparable in each group. ESWL was administered using a piezo-electric lithotriptor (EDAP LT-01), and DT consisted of combined bile salt and terpene administration. Clearance was assessed using a combination of ultrasound and oral cholecystography. Each patient was followed up for 6 months and those with less than 50 per cent clearance at the end of 6 months were considered failures.

		Clearance		
Group	*n*	Total	Partial (>50%)	Failures
ESWL	11	0	0	11
DT	10	1	1	8
ESWL+DT	10	5	2	3

The number of patients with total or partial clearance in the ESWL+DT group was significantly greater than those in either DT ($P<0{\cdot}02$ using a χ^2 test) or ESWL alone ($P<0{\cdot}05$). ESWL merely fragments gallstones, and DT is essential to achieve fragment clearance. This study demonstrates for the first time that gallstone clearance following ESWL appears to be DT dependent, and combination of the two modalities is more potent than DT alone.

Does selective peroperative cholangiography result in missed common bile duct stones?

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A prospective randomized trial was undertaken to determine if selective peroperative cholangiography resulted in greater morbidity and mortality from missed common bile duct stones. Two hundred and eighty-five patients without indications for common bile duct exploration were randomized blindly into two groups. Group 1 underwent peroperative cholangiography and group 2 did not.

All patients were sent a questionnaire at least 3 years after surgery and 218 of those still living responded (80 per cent). One hundred and thirty-two (60·6 per cent) had peroperative cholangiography. There had been 11 deaths from unrelated causes.

The results showed that routine peroperative cholangiography revealed an unsuspected common bile duct calculus in 12·1 per cent of patients. None of group 2 presented with retained common bile duct stones.

No difference between the two groups was found for postoperative dietary habit, dyspepsia, pain, flatulence, diarrhoea, pale stool or dark urine. One patient in group 1 had endoscopic removal of a retained common bile duct calculus 16 months after cholecystectomy.

It is concluded that peroperative cholangiography does not influence morbidity and mortality from cholecystectomy in selected cases and may be omitted in the absence of clinical indications for common bile duct exploration.

Minimal surgery for symptomatic gallstones: a safe, new procedure in high risk patients

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Cholecystectomy is associated with a mortality rate of up to 10 per cent in elderly patients. To reduce risk, a combined radiological and endoscopic procedure was introduced. Patients over 60 years old who were considered at high risk were selected for this study. The gallbladder was identified using B-mode ultrasonography, and cholecystotomy was performed under local anaesthesia through a 3 cm incision. A specially designed catheter was introduced into the gallbladder through which endoscopic ultrasonic contact lithotripsy was performed. At operation stone clearance was confirmed endoscopically and using completion cholecystography. Catheter drainage was continued for 7 days until a further cholecystogram confirmed clearance. The procedure was attempted in 13 patients (mean age 72 years) with symptomatic gallstones, all had concomitant cardiovascular or malignant disease.

Successful removal of all stones, under local anaesthesia was possible in 12 patients at the original procedure. In one patient the gallbladder could not be isolated through a mini-incision and formal cholecystectomy was performed under general anaesthesia. The procedures were well tolerated, and cholecystography at 7 days confirmed complete stone clearance in all. Apart from two patients who had persistent bile leaks for 30 and 65 days after catheter removal, there were no other complications. All patients are symptom free at a mean follow-up of 15 weeks, with no recurrent stones.

The new technique of sonographically guided mini-cholecystotomy and endoscopic lithotripsy allows effective treatment of gallstones under local anaesthesia, as a short-stay procedure. A specially designed retention catheter facilitates this procedure, by preventing peritoneal spillage, and by fixing the gallbladder fundus to the anterior abdominal wall.

The development and reversibility of T lymphocyte dysfunction in experimental biliary obstruction

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Patients with obstructive jaundice have a high incidence of infective complications following surgery. This may be related to changes in cell-mediated immunity. We have studied the effect of experimental biliary obstruction and biliary drainage on immune function. Cell-mediated immunity was assessed by a phytohaemagglutinin stimulation test of splenic lymphocytes. All experiments used adult female Wistar rats.

Group I animals had bile duct ligation (BDL) performed and were killed at 7 day intervals up to 35 days.

Group II animals had BDL for 21 days followed by periods of internal biliary drainage (ID) up to 28 days.

Group III animals had biliary obstruction followed by external biliary drainage (ED) for 14 days. Results are given in the *Table*

Animal group	n	Scintillation	Animal group	n	Scintillation
1 Control	10	27 193 10 027	II 7d ID	10	12 974 3 101*
Sham	10	20 806 7 584	14d ID	9	21 748 2 809
7d BDL	10	25 797 9 284	28d ID	10	34 110 10 346
14d BDL	10	14 744 7 042*			
21d BDL	10	10 927 5 880*	III 14d ED	9	15 014 2 879**
35d BDL	10	7 415 5 172*			

Mean scintillation, 95 per cent confidence limits, * P0 05 compared with controls t test, ** P0·05 compared with 14d ID t test

All the BDL groups had elevation of bilirubin and both ID and ED groups had return of bilirubin to within the normal range. The results demonstrate that depression of cell-mediated immunity in biliary obstruction is progressive, with significant depression after 14 days. This is restored by 14 days ID but not 14 days ED. This may explain why preoperative external biliary drainage does not reduce the incidence of infection in jaundiced patients.

Effect of CCK-PZ and secretin on pancreatic enzyme concentration and severity of experimental pancreatitis in cats

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Pancreatitis occasionally complicates endoscopic retrograde cholangiopancreatography (ERCP). If pancreatitis is due to endogenous enzyme release its severity could be limited by prior reduction of pancreatic enzyme concentration.

Cats were pretreated with intravenous cholecystokinin-pancreozymin (CCK-PZ) and secretin. Controls received saline Pancreatic enzyme concentration was then determined. Oedematous pancreatitis was induced in six pretreated (group A) and six control cats (group B) by bile salt and enterokinase pancreatic duct perfusion Haemorrhagic pancreatitis was induced in five pretreated (group C) and five control cats (group D) by duct perfusion plus intravenous prostaglandin E_2. Histological severity of pancreatitis and residual exocrine function were measured after 24 hours.

Pretreatment reduced pancreatic enzyme concentration from 125 926 (16 306) U/g to 76 483 (9614) U/g for amylase ($P < 0 05$), 658 121 (15 327) U/g to 433 775 (75 435) U/g for lipase (n.s) and 8261 (1479) µ/g to 6288 (565) U/g for trypsinogen (n.s.). Pretreatment had no effect on histological pancreatitis score: 11 (3–54) for group A, 10 (2–29) for group B, 30 (24–41) for group C, and 33 (9–41) for group D. Residual exocrine pancreatic function was also unaffected by pretreatment.

The severity of haemorrhagic pancreatitis correlated with pancreatic lipase concentration ($r = 0 66, P < 0 05$) but not amylase or trypsinogen.

Pretreatment with CCK-PZ and secretin is unlikely to protect patients from post-ERCP pancreatitis Specific reduction of lipase concentration may be more effective.

Does CT angiography predict the clinical course of pancreatic necrosis?

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In patients with severe acute pancreatitis computed tomography (CT) angiography indicates the extent of pancreatic and peripancreatic ischaemia, but its prognostic value remains unclear. A weighted scoring system which quantifies the extent of pancreatic and peripancreatic necrosis visualized by CT angiography was compared with clinical outcome in 27 patients with severe acute pancreatitis and a collection containing ischaemic tissue >5 cm diameter. CT angiography was carried out from 2 to 42 days from the commencement of pancreatitis and was scored by 2 radiologists Ten patients had a pancreatic abscess (pus was the dominant element in the collection) and 17 had pancreatic necrosis (necrotic tissue the dominant element). Six patients died and 19 received urgent intervention (surgery in 12 and percutaneous drainage in seven).

Outcome	Score (range and median)		Outcome	Score (range and median)	
Survived	1–12 (6)	$> P < 0 04$*	No intervention	4–9 (6)	> n s *
Died	5–11 (10)		Needed intervention	1–12 (8)	

* Mann–Whitney U test

Thirteen patients who needed intervention scored >6, compared with 2 (25 per cent) of patients who did not receive intervention. CT angiography enables selection of patients with pancreatic necrosis who are at high risk of a deteriorating course, but factors other than the extent or site of necrosis are important to outcome

Beneficial effects of taurolidine in experimental pancreatitis

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Taurolidine, a derivative of formaldehyde and the amino acid taurine, has potent antiendotoxin and antimicrobial effects *in vitro* This study assessed the effect of taurolidine in a well-described model of acute pancreatitis.

Sixty four male Wistar rats (250 g) were studied Pancreatitis was induced by intraductal administration of 50 µl of a 4 per cent sodium taurocholate solution at a pressure of 25 cm of water. Taurolidine (100 mg/kg) or saline was administered intravenously immediately following pancreatitis Animals were randomly allocated to group A, sham operated controls; group B, i.v. taurolidine administration; group C, pancreatitis and i.v taurolidine administration; and group D, pancreatitis and i v. saline administration Serum amylase levels and septicaemia on blood culture (BC) were assessed at 4 h Survival was documented at 1 week. Data were analysed by χ^2 and Student's t test.

Group	n	Mean amylase (IU/l)	BC positive	Survival
A sham	5	3 715	0	5
B taur	5	3 636	0	5
C pancr + taur	19	7 040	0	18*
D pancr + saline	35	12 525	20%	5

* $P < 0 001$ for C *versus* D

There was no significant difference in serum amylase levels between all groups. Taulonidine administration after bile salt induced pancreatitis significantly improved survival These data suggest that taurolidine may have a therapeutic role in acute pancreatitis.

A multicentre controlled clinical trial of high volume fresh frozen plasma therapy in prognostically severe acute pancreatitis

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Fresh frozen plasma (FFP) therapy may improve survival in acute pancreatitis The proposed mechanism is the replenishment of specific proteins, particularly α_2 macroglobulin (A_2M), a centrally important antiprotease.

In a multicentre trial, patients with prognostically severe pancreatitis (three or more adverse Glasgow prognostic criteria) are randomized to receive 24 units of FFP or a similar volume of human albumin solution (colloid control) during the first 72 hours. Antiproteases and other proteins are measured on days 1, 3 and 7.

To date 265 patients with pancreatitis have been referred of which 55 with prognostically severe disease were randomized. There were seven deaths in the colloid control group (29 per cent) and four in the FFP group (15 per cent). The concentrations of proteins showing a positive acute phase response (C-reactive protein, α_1 antiprotease α_1 antichymotrypsin, fibrin degradation products, D-dimer) were not influenced by FFP therapy. The exception was plasma fibrinogen, concentrations of which were higher on day 3 in the FFP group ($P < 0·02$). The concentrations of proteins which showed a negative acute phase response (A_2M, antithrombin III, fibronectin) were increased by FFP therapy so that on day 3 concentrations were higher in the FFP group ($P < 0 001$, $< 0 01$, $< 0·05$).

The confirmation that FFP therapy supplements declining concentrations of negative acute phase proteins including A_2M may be important. The trial will continue to see if significant benefit results.

Photodynamic therapy for malignant dysphagia

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Photodynamic therapy (PTD) is an exciting method of selectively treating carcinoma using a photosensitizing drug (haematoporphyrin derivative (HpD)) activated by laser light. Previous attempts to treat oesophageal lesions have been hampered by failure to deliver light uniformly. We have designed a new light delivery system which overcomes this and have assessed its effect in eight patients (age 25–70, nine treatments) with inoperable malignant dysphagia. Our system uses a polytetrafluoroethylene diffuser on an optical fibre to scatter light cylindrically. A modified Eder–Puestow dilator with a perspex window surrounds this so that circumferential tumours receive uniform light energy density plus or minus 10 per cent. HpD (4–5 mg/kg) was given intravenously 48 h before light delivery (50–150 J/cm², 630 nm light). Assessment before and after treatment was by dysphagia score (0–5) and minimum diameter on quantitative barium examinations:

	Dysphagia score (n=9)		Diam (mm) (n=6)	
	Before	After	Before	After
Median	*3	*5	*3·5	*10·5
Range	0–4	1–5	2·6–5	4·9–15

* Wilcoxon test, $P>0·01$

All patients except one improved their score, maintaining it until death (3 days to 9 months later), with total relief of dysphagia in five. One patient was perforated by instrumentation 4 days after PDT and subsequently died. There were no other complications. One patient has had a complete remission of microscopic tumour recurrence.

Instrumentation of the stricture should be avoided soon after PDT. Using this light delivery system we have demonstrated that PDT is a useful palliative treatment.

Nucleolar organizer region scores in surveillance of Barrett's metaplasia

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While the risk of carcinoma of the oesophagus in patients with Barrett's oesophagus is low, endoscopic surveillance is advocated. To identify at-risk patients this study assesses the role of nucleolar organizer region (NOR) activity. NORs, which are loops of DNA encoded for ribosomal RNA, have been related to mitotic rate and are identified by means of an argyrophilic histological technique.

Eighty-three tissue sections from 35 patients with Barrett's mucosa were studied in the following groups: (i) metaplasia ($n=25$), (ii) dysplasia ($n=44$, mild 19, moderate 17, severe 8); and (iii) adenocarcinoma ($n=14$). The sections were randomized, coded and NOR activity was scored by two independent observers. The results are shown in the *Table*.

		Dysplasia			
	Metaplasia	Mild	Moderate	Severe	Carcinoma
Barrett's oesophagus ($n=21$)	5·3 (1·2)	6·9 (1·7)	7·8 (1·9)	8·1 (0·9)	
Barrett's epithelium + carcinoma ($n=14$)	5·5 (0·9)	7·2 (0·6)	7·9 (1·7)	11·5 (3·7)	13·9 (5·1)
All cases ($n=35$)	5·3 (1·2)***	7·0 (1·5)**	7·9 (1·8)**	10·2 (3·3)	13·9 (5·1)***

** $P<0·001$ *versus* severe dysplasia; *** $P<0·001$ *versus* all groups

The NOR score correlated well with the histological grading of dysplasia. The NOR score was significantly higher in patients with dysplasia associated with carcinoma than in patients with dysplasia in benign Barrett's oesophagus ($P<0·01$). This may provide a reproducible means of quantifying progression and risk in serial follow-up.

Randomized controlled study of the gastrin receptor antagonist proglumide in the treatment of gastric cancer

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In spite of advances in surgery and anaesthesia there has been no improvement in the prognosis of gastric carcinoma over the last 70 years, and there is no safe and effective form of treatment for advanced disease. Gastrin is known to be a trophic agent to gastric mucosa, and proglumide has been shown to inhibit the growth of gastric carcinoma cell lines and xenografts[1].

To investigate the effect of proglumide in patients with advanced gastric cancer, 85 patients were randomized after stratification for severity of disease to a treatment group which received proglumide 800 mg q.d.s., or to join an untreated control group. Patients were followed up at regular intervals using time of death from randomization as the end point. The control and treatment groups were age-matched, but there was an excess of men in each group. The mean follow-up to date is 40 weeks and 44/85 (52 per cent) of the patients have died. The median survival in the control group was 170 days (95 per cent confidence interval 65–275 days), whilst in the treated group the medial survival was 204 days (95 per cent confidence interval 118–289 days), the generalized Wilcoxon statistic = 2·04, $P=0·15$.

These data suggest that there may be a survival advantage to be gained from using gastrin receptor antagonists in the therapy of gastric cancer.

1 Beauchamp RD, Townsend CM, Singh P, Glass EJ, Thompson JC. Proglumide, a gastric receptor antagonist, inhibits growth of colon cancer and enhances survival in mice. *Ann Surg* 1985; **202**: 303–9.

Hepatic perfusion index: pause for thought

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The hepatic perfusion index (HPI) derived by dynamic hepatic scintigraphy (DHS) predicts the presence of micrometastases in man. We have shown similar alterations in the HPI of rats with hypervascular hepatic tumours and have demonstrated that these changes resulted from a decrease in portal venous inflow (PVI) and arteriovenous shunting. We have now repeated these studies on hypovascular tumours which are more representative of those found in man.

Hepatic and systemic haemodynamics, arteriovenous shunting and HPI were determined in rats 2, 6, 10 and 20 days after intraportal administration of 10° HSN sarcoma cells. Overt hepatic tumour was present at 20 days. However the mean(s.d.) HPI in animals with tumour (47·2(4·1)) was significantly greater ($P<0·002$, Student's t test) than in controls (35·2(2·97)) at 10 days and remained elevated at 20 days. Hepatic artery flow was unchanged throughout the study but PVI was significantly decreased ($P<0·001$) at 10 and 20 days. No arteriovenous shunting occurred during the growth of the tumour.

These results indicate that in slow growing hypovascular hepatic tumours, changes in the HPI occur late in their development and are related to a reduction in PVI, suggesting that DHS may not predict very early tumours in man.

Immunohistochemical study of a new monoclonal antibody, MC3, in pancreatic tissues

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Adenocarcinoma of the pancreas has a low 5-year survival rate. Diagnosis is often late when there is minimal chance of cure. Radiolabelled monoclonal antibodies may offer a new approach in management. The aim of this study was to assess the immunohistochemical pattern of staining in normal and diseased pancreas using a new murine monoclonal antibody, MC3, raised against a human colorectal carcinoma.

Formalin-fixed, paraffin-embedded tissue sections from patients with adenocarcinoma of the pancreas ($n=14$), acute pancreatitis ($n=10$), chronic pancreatitis ($n=4$), gastrinomas ($n=4$), insulinomas ($n=2$) and normal pancreas ($n=11$) were stained with MC3 using the avidin–biotin peroxidase method. Staining was assessed according to the cytological distribution and the percentage of cells staining (none, 10 per cent, 10–50 per cent, >50 per cent) The results are shown in the *Table*.

		Staining with MC3			
	n	None	<10%	10–50%	>50%
Normal pancreas	11	8	3		
Chronic pancreatitis	4	4			
Acute pancreatitis	10	10			
Adenocarcinoma	14			3	11
Gastrinoma	4	3	1		
Insulinoma	2	1	1		

Staining was localized to the apical membrane, superficial mucin and supranuclear cytoplasm of tumour cells Over 50 per cent of cells staining was taken as a positive level (χ^2 normal *versus* carcinoma, $P<0{\cdot}001$, pancreatitis *versus* normal $P<0{\cdot}001$) We conclude that MC3 recognizes a tumour associated antigen which on immunohistochemical staining is highly expressed on adenocarcinomas of the pancreas when compared with normal and benign pancreatic tissue.

Serum gastrin concentrations are elevated in colorectal cancer

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Gastrin is an established trophic factor for benign and malignant colonic epithelial cells We have measured fasting serum gastrin levels by radioimmunoassay in 62 patients with colorectal cancer and in 18 age-matched patients who had a normal colonoscopy and no evidence of malignancy. In colorectal cancer patients the median serum gastrin level was 49·35 pg/ml (range 7·5–1300·0) and in patients with a normal colonoscopy 36·6 pg/ml (range 5·5–53·3), $P=0{\cdot}005$ (Mann–Whitney *U* test). Among the cancer patients, 26 per cent had elevated serum gastrin concentrations (greater than mean +2 s.d. of normals).

To determine the origin of the elevated serum gastrin, 54 colorectal cancer patients had tumour-draining mesenteric vein blood samples taken at surgery before their colonic resection and a peripheral venous sample was taken simultaneously Median gastrin concentration in mesenteric vein blood was 45·4 pg/ml (range 6·0–1100·0) and in peripheral blood was 49·3 pg/ml (range 7·5–1300·0), the values being very similar in individual patients (correlation coefficient $r=0{\cdot}99$)

In eight patients who underwent a curative resection, postoperative fasting gastrin levels were similar to preoperative levels ($r=0{\cdot}977$), confirming that the hypergastrinaemia in colorectal cancer patients is not due to tumour production but may be a causative factor in relation to tumour aetiology.

Increasing tumour capillary permeability enhances tumour uptake of antibody–isotope conjugate

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Treatment of colorectal liver metastases with antibody–isotope conjugates (AIC) is limited by the poor ratio of tumour to normal tissue uptake. We have improved tumour uptake of AIC by regional perfusion of two agents which increase capillary permeability – histamine and leukotriene C_4 (LTC_4)

Human colorectal carcinoma xenografts (LS174T) were grown in hind limbs of athymic rats to derive their circulation from the femoral artery Anti-carcinoembryonic antigen monoclonal antibody (A5B7) conjugated with ^{131}I was infused either regionally via the femoral artery ($n=12$) or systemically via a lumbar vein ($n=12$) In a further 19 animals the AIC was mixed with histamine ($n=12$, 10 mg/kg) or LTC_4 ($n=7$, 25 μg/animal) and delivered via the regional cannula. The cannula was removed after 1 h and the animal recovered After 48 h the animal was killed. Tumour and liver were weighed and γ activity measured in a well counter. The results are shown in the *Table*.

	Tumour:liver ratio (counts/g)	Significance of difference compared with systemic delivery
Systemic delivery	1·22(0·40)	–
Regional delivery	1·62(0·56)	n.s.
Histamine	3·26(0·89)	$P<0{\cdot}01$
LTC_4	2·88(0·71)	$P<0{\cdot}05$

Values mean (s.d.)

Regional delivery slightly increased tumour AIC uptake 33 per cent However, addition of histamine or LTC_4 produced a three-fold increase in AIC uptake compared with systemic delivery.

Chromosome 5 deletion map around the gene for familial adenomatous polyposis in non-familial colorectal cancer

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The familial adenomatous polyposis (FAP) gene maps to chromosome 5q21. Somatic mutation of both copies of this putative tumour suppressor gene is hypothesized to occur in sporadic colorectal carcinomas but supporting evidence is insubstantial. We report a detailed deletion map of chromosome 5 in 118 sporadic colorectal carcinomas Using 12 previously mapped polymorphic DNA probes, matched tumour and blood leukocyte DNA preparations were analysed for loss of constitutional heterozygosity close to the FAP gene and at loci spanning chromosome 5. Allele loss at any heterozygous locus was noted in 51 of 114 tumours (45 per cent), rising to 54 per cent (35/65) where 5q21 probes flanking the FAP gene were both heterozygous. These losses comprised 18 interstitial deletions, five long arm losses, four mitotic recombinations and one whole chromosome loss The remainder could not be assigned due to limited heterozygosity. Patterns of allele loss were consistent with specific involvement of a gene located between probes C11P11 and YN548, which closely flank the FAP gene Allele loss did not correlate with Dukes' classification, suggesting early, perhaps causative, involvement.

This study demonstrates the nature and frequency of chromosome 5 allele loss in sporadic colorectal cancer The data suggest specific involvement of the FAP gene itself.

Site-dependent sensitivity of Haemoccult® screening: implications for test design

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Haemoccult® (Norwich Eaton Ltd., Newcastle upon Tyne, UK) utilizes the pseudoperoxidase activity of haematin to detect faecal occult blood Non-haemolysed blood (fresh rectal bleeding) or excessively degraded haemoglobin (proximal colonic bleeding) is thought to produce false negative reactions.

We report the site distribution of cancers missed by Haemoccult in a screening study for colorectal neoplasia. Haemoccult tests were completed on 32 213 subjects (age range 50–74 years); 2·1 per cent were positive Further investigation revealed 94 carcinomas (rectum, 16; sigmoid/descending colon, 63; transverse colon, six; ascending colon and caecum, nine) Twenty-four carcinomas have presented in the 2-year period following a negative test; these are presumed to have been missed by Haemoccult (rectum seven, sigmoid/descending colon eight, transverse colon two, ascending colon and caecum seven)

These data suggest that Haemoccult misses 30 per cent of rectal cancers, 12·5 per cent of sigmoid/descending colon cancers, 25 per cent of transverse colon cancers and 44 per cent of those in the ascending colon or caecum. A greater proportion of missed cancers were rectal ($\chi^2=4{\cdot}00$, $P<0{\cdot}05$) or in the caecum/ascending colon ($\chi^2=8{\cdot}59$, $P<0{\cdot}01$) than in the sigmoid/descending colon.

Haemoccult varies in sensitivity from 56·2 per cent for right-sided cancers to 87·5 per cent for sigmoid/descending colon cancers. Tests not dependent on haematin may demonstrate increased sensitivity for rectal and right-sided neoplasia

Increased compliance rates anticipated with the use of self-administered tests for faecal occult blood (FOB) screening are not observed in a randomized controlled trial

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Compliance is a major determinant of the efficacy of screening for colorectal cancer. Performance of conventional tests requiring manipulation of faeces is thought to be a major factor causing non-compliance[1]. New guaiac based self-administered tests (SATs) like Early Detector (ED) and Coloscreen Self-Test (CST) require little or no direct manipulation of faeces.

To test the hypothesis that compliance could be improved by using SATs a randomized controlled trial was conducted in the general practice setting comparing compliance using two SATs, ED and CST with Haemoccult® (Norwich Eaton Ltd., Newcastle upon Tyne, UK) (H). The effect of dietary restriction on compliance and positive rates for the three tests was also evaluated. A total of 1847 individuals were randomized by household into six groups (each receiving one test, with or without dietary restrictions). Overall compliance was 53 per cent. Logistic regression was used for the analysis to account for interaction between predictors of compliance. Neither test method nor dietary restriction had significant effects on compliance. The positivity rate was significantly greater for ED (mean = 15·2 per cent) than H (mean = 4·1 per cent) or CST (mean = 2·0 per cent). Furthermore, for H positivity was not reduced by dietary restriction.

The results show that the use of SATs failed to produce the anticipated increase in compliance rates. Faecal manipulation and dietary restriction are unlikely to be significant obstacles to compliance.

1. Farrands PA, Hardcastle JD, Chamberlain J, Moss S. Factors affecting compliance with screening for colorectal cancer. *Community Med* 1984; 6: 12–19

Colorectal cancer screening: does a false negative result adversely affect tumour stage?

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Haemoccult® (Norwich Eaton Ltd., Newcastle upon Tyne, UK), a faecal occult blood test, has a false negative rate for cancer of 25–35 per cent in screening studies. It is of concern that the reassurance offered by such a result will delay presentation once the cancer becomes symptomatic.

We have compared tumour stage in those cancers thought to have been missed in a Haemoccult screening study for colorectal neoplasia with those diagnosed in a control group not offered the test. Twenty-four carcinomas have presented symptomatically in 31 536 subjects (age 50–74 years) following negative Haemoccult tests in the 2-year interval before being offered a retest (interval cancers). Seven (29 per cent) were Dukes' A, five (21 per cent) were Dukes' B, six (25 per cent) Dukes' C and six (25 per cent) Dukes' D.

In the control group (61 996 persons) 164 cancers have been diagnosed (16 (10 per cent) Dukes' A, 53 (32 per cent) Dukes' B, 55 (33·5 per cent) Dukes' C and 40 (24 per cent) Dukes' D).

Significantly more interval cancers were at Dukes' A than control group cancers ($\chi^2 = 7{\cdot}35$, $P < 0{\cdot}01$); there was no statistical difference for other tumour stages.

Whilst accepting a possible selection bias in favour of the interval group, these findings suggest that a false negative Haemoccult result does not adversely affect tumour stage in a colorectal cancer screening programme.

Crypt cell production rate (CCPR) of the colon following chemical carcinogenesis administration

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It has been proposed that there is a cause and effect relationship between the CCPR, tumour formation and established colorectal cancer in experimental animals (and by extrapolation in humans) but the evidence is incomplete.

In order to study this further, the CCPR was determined in a cohort of 75 female Wistar rats undergoing carcinogenesis using 1,2-dimethylhydrazine (DMH) 40 mg/kg weekly for 5 weeks, control animals were injected with the DMH carrier. The CCPR was determined after giving 1 mg/kg vincristine intraperitoneally followed by serial sacrifice of three animals per time point at 1, 1·5, 2, 2·5 and 3 h. All stathmokinetic analyses were performed by an independent blind observer.

At 10 weeks no animals had colorectal tumours compared with 80 per cent at 25 weeks. Before DMH the mean (s.e.m.) CCPR was 3·31 (0·55) cells/crypt/h. At 10 weeks this was 3·63 (0·89) in controls and 7·64 (1·09) in DMH animals ($P < 0{\cdot}001$, Student's *t* test) and 2·99 (0·43) *versus* 1·05 (0·68) respectively at 25 weeks.

Although the colonic CCPR was increased after DMH, it was not sustained into tumour formation. This may suggest that changes in CCPR previously observed are linked to drug administration rather than tumour formation itself.

Immunoscintigraphy in the detection of recurrent colorectal cancer: evaluation in conjunction with computed tomographic scanning

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Immunoscintigraphy using an indium-labelled anti-carcinoembryonic antigen monoclonal antibody, C46 (Amersham International), has been compared with computed tomographic (CT) scanning in the detection of abdominal and pelvic recurrence from colorectal cancer. The detection of liver metastases was not evaluated.

Thirty patients with suspected recurrent carcinoma have been imaged using both techniques. All images were read blindly, no clinical information being available to the observers. Eighteen patients had 22 individual recurrences (12 pelvic and 10 abdominal), 15 confirmed by histology, two by operation and five by disease progression. Twelve patients, negative for recurrence, were followed up for a median time of 16 months (range 6–19 months). The results are shown in the *Table*

	Detection of recurrence	
	Sensitivity (lesions detected) (%)	Specificity (%)
Immunoscintigraphy	82	36
CT scan	68	95

Because of the absence of fat around the bowel in the abdomen, CT scanning was less accurate in the abdomen than in the pelvis. In five patients recurrence was missed by CT scan and in four of these it was detected by immunoscintigraphy, three of these four patients having abdominal disease. Immunoscintigraphy detected 90 per cent of abdominal recurrences against 60 per cent detected by CT scan.

Immunoscintigraphy is particularly sensitive in the identification of recurrent colorectal cancer within the abdomen where CT scanning is less accurate.

Endoscopic transanal resection of rectal tumours: preliminary report

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Abdominoperineal resection and anterior resection are major operations for elderly frail patients or for those requiring palliation. Endoscopic transanal resection (ETAR) of rectal tumours, using a large diameter resectoscope, is by contrast a relatively simple and inexpensive procedure. We have performed 137 ETARs in 81 patients with a 30-day mortality of 11·1 per cent and postoperative complications occurred after 21 of the 137 procedures (15·3 per cent).

Thirty-one (38 per cent) were resected for palliation. In this group ETAR abolished or improved rectal bleeding in 66 per cent of patients, diarrhoea in 77 per cent of patients, faecal incontinence in 50 per cent of patients and rectal pain (including tenesmus) in 50 per cent of patients.

Twenty-three patients (28 per cent) were treated for large benign rectal polyps. Symptoms were universally abolished and the technique is particularly suited to the management of these patients.

Twenty-eight patients with theoretically 'curable' rectal cancer were resected with a 78 per cent survival at 1 year. Long-term survival and recurrence rates in this group remain to be assessed, but 21 have died with a median survival of 13 months.

ETAR is a useful repeatable technique for treating selected patients with rectal tumours. In elderly patients it has an acceptable mortality and morbidity.

Safe parameters for contact Nd:YAG laser palliation of colorectal cancer

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Non-contact Nd:YAG laser vaporization of advanced colorectal cancer is associated with perforation rates of up to 7 per cent. Contact Nd:YAG laser probes may produce more precise thermal effects. The tissue effects of contact laser probes have been investigated.

Contact Nd:YAG laser insults were inflicted on human colorectal carcinomas and adjacent normal bowel wall *in vitro*. Laser powers of 5–30 W in pulses of 1–5 s produced total energies of 5–125 J.

Depth of tissue vaporization and coagulation in normal bowel wall and tumour were not significantly different at all energies ($P > 0{\cdot}1$, Mann–Whitney *U* test). In normal bowel, vaporization was confined to mucosa and submucosa at total energies <30 J. At energies of 30–50 J, 18/39 lesions (46 per cent) penetrated the muscularis and 3 of 39 (8 per cent) produced perforation. At energies >50 J 26 of 57 lesions (46 per cent) penetrated the muscularis and a further 26 of 57 (46 per cent) produced perforation. Ulcerated pale tumour was more resistant to vaporization than other tumour tissue, mean (s.d.) vaporization depths being 1·32 (0·2) mm and 2·74 (0·58) mm respectively at 75 J total energy ($P < 0{\cdot}02$).

Contact laser probes produce predictable depths of tissue vaporization and coagulation. Ulcerated pale colorectal tumour is relatively resistant to vaporization. There is a significant risk of bowel perforation at total energies exceeding 50 J.

Transcription of *c-myc* mRNA and protein product is a potential prognostic indication in colorectal cancer

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Variation in oncogene expression may be one of the ways in which a tumour acquires ever more malignant characteristics.

Southern blotting using a DNA probe recognizing all three exons of the *c-myc* gene showed no evidence of DNA amplification in 12 fresh colorectal tumours of all four stages of Dukes' classification. However, quantitative dot blotting of mRNA transcript revealed a variation from unity to eight-fold when compared with a high *c-myc* expressing cell line, COLO 320.

Varying levels of the nuclear expressed protein product in *c-myc*, p62 *c-myc* in archival paraffin-embedded material were demonstrated by a flow cytometric assay[1]. A double labelling technique was used to quantify the protein of extracted nuclei with a monoclonal antibody (MYC1 6E10) and a second fluorescein labelled immunoglobulin and quantitated by flow cytometry. Protein levels correlated well using this technique to mRNA levels ($r = 0{\cdot}8$; $P < 0{\cdot}002$).

A preliminary study in 83 patients revealed low levels of p62 *c-myc* correlated to survival in patients followed up to 5 years (log rank analysis $\chi^2 = 4{\cdot}69$; $P = 0{\cdot}03$, d.f. = 1).

It is concluded that p62 *c-myc* expression can be quantitated by flow cytometry and correlates with mRNA levels and appears to be related to prognosis.

1. Watson IV, Sikora K, Evan GI. A simultaneous flow cytometric assay for *c-myc* oncoprotein and DNA in nuclei from paraffin embedded material. *J Immunol Methods* 1983; **83**: 179–92.

Intraoperative detection of cancer using radiolabelled antibodies: clinical use and experimental evaluation

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Radiation detectors may allow small cancer deposits to be detected intraoperatively following radiolabelled antibody administration. A clinical evaluation was carried out on 16 patients with colorectal tumours (14 cancers, one adenoma, one lipoma) with the indium (^{111}In)-labelled monoclonal antibody ICR2, recognizing the tumour associated epithelial membrane antigen (EMA). At operation counting was carried out (3 × 20 s/site) over the primary cancers and any palpable mesenteric nodes (all <1 cm diameter). The tumour/normal colon ratio (T/NC) of counts *in vivo* was $>1{\cdot}5:1$ in nine of the 14 patients with cancer (mean(s.d.) 1·83 (0·21):1), 0·96:1 and 1·06:1 in the two patients with benign tumours and node/normal colon ratio higher in those containing metastases (mean (s.d.) 1·7 (0·06):1 *versus* 0·84 (0·33):1, $P = 0{\cdot}017$). EMA expressing cancers had higher T/NC ratios on well counting (mean(s.d.) 2·45 (0·65):1 *versus* 1·30 (0·25):1, $P = 0{\cdot}005$).

Following clinical evaluation an abdominal tumour model was used to assess the limitations of this technique. Spheres of 0·5–10 ml representing tumour deposits were suspended in a tank of ^{111}In representing background or normal tissue radioactivity. The ratio of radioactivity in the tumour to that of the background was varied from 2:1 to 8:1. The tumour was considered to be detectable if the mean counts over the tumour exceeded that of the background by two standard deviations. At 2:1 only tumours of 10 ml could be detected. At 8:1, 1 ml tumours were detected.

We conclude that small tumour deposits may be detected intraoperatively with indium-labelled monoclonal antibodies but that high uptake ratios (T/NC) are required.

Pretreatment with MPA enhances actions of cytotoxic drugs on MCF-7 cells: a possible mechanism of such action?

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Pretreatment with medroxyprogesterone acetate (MPA) enhances the response of breast cancer cells to cytotoxic agents[1]. Evidence to support this was presented to the SRS in July 1988. MPA increases the cytotoxicity of methotrexate (MTX) and vincristine[2] as well as Adriamycin® (ADR) (Farmitalia Carlo Erba, St. Albans, UK) and this action of MPA seems to be independent of its growth inhibitory effect. A possible mechanism may be the reduction of receptor levels.

To investigate this possibility, the receptor negative breast cancer cell line MDA-MB-231 was used. The cells were exposed to MPA or control medium for 48 h, followed by chemotherapy drug (ADR or MTX) or control medium for 24 h. The washed cells were then allowed to proliferate for 3–4 days before being harvested and counted. The effect of MPA at a concentration of 40 nM on these receptor negative cells was not significant ($P = 0{\cdot}1$) and pretreatment with MPA did not enhance the cytotoxic effect of MTX or ADR.

The findings of enhancement of cytotoxicity of MTX and ADR by MPA on receptor positive cells, while no such action was obtained on receptor negative cells, suggests that this action of MPA may be receptor mediated.

1. Shaikh NA, Owen AM, Ghilchik MW, Braunsberg H. Actions of MPA on the efficacy of cytotoxic drugs – studies with human breast cancer cells in culture. *Int J Cancer* 1989 (in press).
2. Shaikh NA, McNeil JM, Patel K, Ghilchik MW, Braunsberg H. Interactions between E_2, MPA and cytotoxic drugs in human breast cancer cells in culture. *J Steroid Biochem* 1987, **28**(Suppl): 1585.

Stimulation of endogenous production of tumour necrosis factor during intracompartmental therapy with interleukin 2 receptor

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The antitumour efficacy of interleukin 2 (IL-2) is believed to be mediated by generation of lymphokine activated killer (LAK) activity amongst peripheral blood lymphocytes (PBL). This can be measured as enhanced activity to standard target cell lines in direct cytotoxicity assays *in vitro*. Enhanced lytic activity in PBLs is predominantly due to activation of natural killer cells (CD3−, CD16+, LGLs). However, during successful adaptive cellular immunotherapy few cells (1 per cent) of this phenotype infiltrate the tumour, suggesting that direct lysis (as measured in target cell assays) may not be the only mechanism of antitumour activity during LAK therapy.

We have serially analysed tumour necrosis factor α (TNF) in peritoneal cavity fluid during intraperitoneal generation of LAK cells from PBLs. LAK activity was confirmed *in vitro* by demonstration of significantly increased cytotoxic activity to K562 ($P<0{\cdot}01$) and Daudi ($P<0{\cdot}01$) targets. Paired target lysis assays showed good correlation ($r=0{\cdot}58$, $P<0{\cdot}01$, $n=52$) between the sensitivity of these two target cell lines.

Significant stimulation of endogenous TNF production was apparent in all of six treatment cycles studied in five patients (range 22–800 pg/ml). There was no apparent correlation between TNF levels and cytotoxic activity to either target cell ($n=48$).

The full spectrum of biological activity of IL-2r is not reflected by *in vitro* cytotoxicity assays. Antitumour activity may be mediated *in vivo* by a cascade release of cytokines, TNF production may contribute to this activity.

Treatment of liver metastases by cryotherapy

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We have developed a new design of cryoprobe which enables freezing of an intrahepatic lesion with minimal destruction of surrounding tissue. The cryoprobe has a 5 mm diameter shaft and a copper tip through which liquid nitrogen circulates at −196°C. The probe is inserted into the lesion at laparotomy under intraoperative ultrasound control and coolant is circulated producing a sphere of liver destruction, the size of which can be monitored by intraoperative ultrasound.

Eight patients with liver metastases (six colorectal, one carcinoid and one ovarian) have undergone cryotherapy of a total of 42 metastases (range 3–12 metastases/patient), eight of which were impalpable and detectable only by intraoperative ultrasound. All patients were discharged 5–10 days postoperatively and there were no complications. The patient with carcinoid has been relieved of his symptoms of flushing and diarrhoea and in three of four colorectal patients followed up for 3 months serum carcinoembryonic antigen has decreased, in one patient to undetectable levels. Computed tomographic scans have shown defects in the liver substance corresponding to the frozen metastases.

Cryosurgery of the liver using this novel system may provide an alternative techique for the treatment of patients with small numbers of unresectable liver metastases.

Is the use of the cell separator an alternative to transfusion with banked blood during cancer surgery?

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Perioperative transfusion using banked blood worsens the prognosis in patients undergoing cancer surgery[1]. Autologous transfusion utilizing a cell saver avoids this problem but risks the dissemination of tumour cells in the red cell concentrate (RCC). The aim of this study was to determine whether viable tumour cells remained in the RCC after separation using a cell saver.

Units of whole blood were inoculated in duplicate with 4×10^7 cells from four tumour cell lines (breast cancer SKBr3, colon cancer COLO 320; erythroleukaemia K562 and lymphoma DAUDI) and processed using a Haemonetics® cell saver which produces a RCC and a waste saline wash. The saline washes were examined microscopically for tumour cells, 50 ml was spun at 500 *g* for10 min and the pellet cultured in appropriate media at 37°C in 5 per cent CO_2. The RCCs were sedimented on a Ficoll gradient, the 'mononuclear' layer removed, washed, examined for tumour cells and cultured as above.

No tumour cells were seen in the saline washes but all cell lines were easily seen after Ficoll separation of the RCC. All except DAUDI grew within 24 h and continued to grow after passage at 1 week. Occasional cells from the K562 and SKBr3 lines grew from the saline wash, but only after 72 h.

Thus viable tumour cells remain within the RCC after separation. The cell separator cannot be recommended for cancer surgery in which the tumour may be breached.

1. Blumberg N, Heal J, Chuang C *et al.* Further evidence supporting a cause and effect relationship between blood transfusion and early cancer recurrence. *Ann Surg* 1988, **207**: 410–15

p53 gene mRNA expression in breast cancer

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The gene for p53, a 53 kDa phosphoprotein, maps to the short arm of chromosome 17, an important region in breast cancer. p53 has been implicated in cell immortalization and cotransformation and as an anti-oncogene.

Since p53 protein is short-lived, p53 messenger ribonucleic acid (mRNA) merits study. We therefore examined p53 mRNA expression in 49 untreated and 14 tamoxifen-treated consecutive breast cancers (where sufficient tissue was available) and in breast cancer cell lines. Total RNA fixed to nylon membranes was probed using a radiolabelled cDNA probe for p53. The resulting northern blot autoradiographs allowed qualitative and quantitative measures of p53 mRNA.

The cell lines MCF7, T47D and MDAMB231 all exhibited four species of p53 message; breast tumour tissues yielded only one of these four, a 2·8 kb mRNA. This message was detected in 28 of 49 (57 per cent) untreated and seven of 14 (50 per cent) tamoxifen-treated tumours; 15 untreated and three tamoxifen-treated tumours had high levels of mRNA similar to the breast cell lines. However, there was no significant correlation between p53 mRNA expression and tumour size, node metastasis or oestrogen receptor protein.

p53 messenger RNA therefore does not relate to known prognostic parameters in breast cancer.

Relation to mitotic activity of parathyroid adenomas to thallium-201 uptake

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Thallium isotope scintigraphy remains an unpredictable and controversial investigation for the preoperative localization of parathyroid adenomas. The mechanisms of cellular thallium accumulation are not understood. *In vitro* studies[1] suggest that increased uptake of thallium may follow malignant transformation and increased growth rate. A comparison was made between thallium uptake and mitotic activity in 24 parathyroid adenomas. Thallium localization was performed by a standard technique of scintiscanning, while mitotic activity was assessed by DNA analysis with flow cytometry. Adenomas were designated 'correctly' or 'incorrectly' localized by comparing the findings of preoperative scanning with those at surgery including histological examination and mitotic activity designated 'normal' or 'excessive' by reference to the 95 per cent confidence interval for the mean percentage of resting cells in a previous sample of 12 histologically normal parathyroid biopsies.

Fifteen of the 24 adenomas showed excessive mitotic activity and 13 of these (87 per cent) were localized correctly, while of the remaining nine adenomas only five (56 per cent) were localized correctly (χ^2; $P<0{\cdot}01$). There was no significant difference in gland weight between the two groups. These findings provide *in vivo* support for the hypothesis that thallium uptake is related to mitotic activity, and may also explain the limitations of this technique in localizing parathyroid adenomas.

1. Venuta S, Ferrajuolo R, Morrone G, Ambesumpiombato F, Mansi L, Salvatore M. The uptake of 201-thallium in normal and transformed cell lines. *J Nucl Med Allied Sci* 1979, **23**: 163

Age matching improves the results of renal transplantation with older donors

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To cope with rapidly rising transplant waiting lists, kidneys taken from older cadaver donors are increasingly being used, but are unfortunately associated with inferior results, despite good HLA matching[1]. At this centre 40 per cent of locally harvested kidneys come from donors over 50 years of age. One solution not previously tested is the possible benefits of matching donor and recipient age.

In this study we examined the simultaneous effect of donor and recipient age on the graft survival of 141 consecutive first cadaver transplant recipients treated by cyclosporin immunosuppression. Individually there was no significant effect of recipient age whilst donors >50 years were associated with significantly worse ($P<0{\cdot}01$) graft survival than younger donors. Multivariate analysis, taking into account other variables of moderately matched recipients (i.e. dialysis time and type, donor/recipient sex, local/imported kidneys, rejection episodes, max./recent sensitivity, operation time, total ischaemic time, pre- and perioperative transfusion) indicated that donor–recipient age *difference* was the most important variable ($P<0{\cdot}05$) in determining graft success. For donors aged >50 years the 1-year graft was significantly improved when transplanting recipients no more than 5 years older than the donor Donor age should be an important recipient selection criterion in cadaveric renal transplantation

1. Foster MC *et al* Use of older patients as cadaveric kidney donors. *Br J Surg* 1988, **75**: 767–9.

Clinical application of transrectal and abdominal ultrasound with cytology in the detection of recurrent bladder tumours

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Check cystoscopies form a major part of the urological workload Davies *et al.*[1] have shown that the combination of transrectal and abdominal ultrasound will detect 95 per cent of tumour recurrence in the anaesthetized patient. In these patients combination ultrasound and cytology had a sensitivity of 100 per cent. This study was performed to see if similar results could be obtained when the patients were responsible for their own bladder filling and not anaesthetized.

Seventy-six patients (62 men, 14 women) of mean age 66 years (range 41–78 years) with previously known tumours were examined using the Bruel and Kjaer 1846 ultrasound machine using the 4 MHz abdominal probe and the 7 MHz transrectal probe, and urine was sent for cytology The following week cystoscopic examination was performed under general anaesthetic Thirty-seven patients (49 per cent) had recurrent tumour at cystoscopy; 78 per cent were detected by abdominal ultrasound, 73 per cent by transrectal ultrasound and 89 per cent in combination Cytology detected 59 per cent of recurrences and the sensitivity of combination ultrasound with cytology was 95 per cent. The false positive rate was 3 per cent. In certain patients bladder filling was inadequate, and obesity and rectal pathology made abdominal and transrectal ultrasound impossible. All patients stated a preference for ultrasound follow-up.

These results, obtained in an outpatient environment, are similar to those obtained in the anaesthetized patient[1] and will allow us to modify our mode of follow-up of bladder tumours accordingly.

1. Davies AH, Cranston D, Meagher T, Fellows GJ. Detection of recurrent bladder tumours by transrectal and abdominal ultrasound compared with cystoscopy. *Br J Urol* 1989; **64**: 409–11.

Use of damage to the proximal tubules to predict the development of acute tubular necrosis

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It is assumed that delayed graft function results from acute tubular damage. We preserved five canine kidneys with hyperosmolar citrate (HOC) and five with phosphate buffered sucrose (PBS) solutions for 72 h before autotransplantation. Post-preservation biopsies were examined qualitatively and quantitatively using the method described by Burke *et al*[1] in which brush border integrity and numbers of damaged proximal tubular cells are calculated. Using a computerized digitizing tablet tubular and cellular parameters were measured (see *Table*). This indicates that PBS-preserved kidneys show more evidence of tubular injury than those preserved with HOC. Despite biopsy changes the serum creatinine levels of PBS-preserved kidneys are significantly lower than those preserved with HOC

	PBS		HOC		*P* value
Percentage proximal tubules with intact brush border	15·4	(4·4)	18·4	(3·6)	n s
Percentage injured proximal tubule cells	57·2	(12·2)	39·3	(6·5)	n.s.
Luminal area/tubule wall area	0·27	(0·03)	0·46	(0·04)	<0·05
Luminal area/cell area	50·9	(5·5)	76·2	(7·9)	<0·05
Mean maximum creatinine (μmol/l)	285	(20)	990	(206)	<0·05

Values are mean(s.d.)

It is concluded that the likelihood of immediate function is related to factors other than proximal tubular injury during storage.

1 Burke TJ, Arnold PE, Gordon JA, Bulger RE, Dobyan DC, Schrier RW. Protective effect of intrarenal calcium membrane blockers before or after renal ischemia. *J Clin Invest* 1983; **74**: 1830–41.

Relevance of ambulatory monitoring in patients with neurogenic bladder dysfunction and upper tract dilatation

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In neurogenic bladder dysfunction high end filling pressures and poor compliance during fast bladder filling are associated with upper tract dilatation Previous studies have shown important differences between conventional cystometry with artificial filling (CMG) and ambulatory monitoring during natural bladder filling (AM). This prospective study compares the ability of CMG and AM in predicting upper tract dilatation in patients with neurogenic bladders.

Forty-three patients (31 men, 12 women, mean age(s.d.) 30 (26) years) with neurogenic bladder dysfunction and low compliance on CMG were studied by both CMG and AM. The pressure rise during filling on CMG (5±cmH$_2$O; $P<0{\cdot}0001$, Mann–Whitney U test), despite similar filling volumes. Phasic bladder activity was observed more often during AM ($n=35/43$) than during CMG ($n=19/43$; McNemar's $\chi^2+12{\cdot}5$; $P<0{\cdot}001$). In patients with upper tract dilatation both the mean(s.d.) frequency and amplitude of this phasic activity were greater during AM (42(10) contractions/h and 231(98) cmH$_2$O/min) compared with those with normal upper tracts (8·3 (6·7) contractions/h and 156(70) cmH$_2$O/min; both $P<0{\cdot}001$; Mann–Whitney U test) but end filling pressures were not different on CMG.

High end filling pressures were not found on natural filling in neuropathic bladder dysfunction but high frequency phasic activity was found and was closely associated with upper tract dilatation.

β_2-microglobulin: a sensitive index of renal impairment in obstructive jaundice

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Renal impairment is a major factor in the morbidity associated with surgery for obstructive jaundice. To investigate the nature of renal impairment in obstructive jaundice, β_2-microglobulin (β_2M) in serum and urine has been measured by radioimmunoassay in 23 jaundiced patients and 16 controls.

The median preoperative serum β_2M level in jaundiced patients (2·22 mg/l, range 1·054–3·975) was significantly higher than on entry (1·6445 mg/l, range 1·025–1·774, $P<0{\cdot}005$ Mann–Whitney U test). Urinary β_2M concentration and the urine serum ratio did not differ significantly between the two groups. There was a strong correlation between serum bilirubin and serum β_2M ($r_s=0{\cdot}65$, $P<0{\cdot}001$, Spearman rank correlation). The median urine:serum β_2M ratio in jaundiced patients (439, range 7–2988) was significantly higher than in the control patients (18, range 10–3610) on the first postoperative day, and on the third postoperative day (185, range 7–6167 and 13, range 2–4670 respectively, $P<0{\cdot}005$ Mann–Whitney U test).

These results suggest that damage to the proximal renal tubule is a contributory factor in the development of postoperative renal impairment in jaundiced patients. It is suggested that measurement of serum and urinary β_2M is of value in the assessment of renal function in jaundiced patients

Effects of different total parenteral nutrition (TPN) regimens on host antitumour immune responses

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Total parenteral nutrition (TPN) with lipid-based regimens may be detrimental to endogenous antitumour immune mechanisms, the lipid component possibly being responsible for this immunodepression[1] Alternative lipid emulsions may be less suppressive. This study was designed to test this hypothesis

Thirty-six patients with gastrointestinal cancer consented to undergo 7 days of TPN prior to surgery. Each patient was prospectively randomized to receive one of three equicaloric regimens consisting of amino acids, the calories being provided either as glucose alone (G), glucose plus 20 per cent Intralipid (IL) or glucose plus 20 per cent medium-chain triglycerides (MCT). Measurements of natural killer (NK) and lymphokine-activated killer (LAK) cell activities were measured before the start and on day 7 of the study. Mean percentage cytotoxicity against the NK target (K562) and LAK cell targets (DAUDI and COLO) were as shown in the *Table*

	NK *versus* K562			LAK *versus* Daudi			LAK *versus* COLO		
	G	IL	MCT	G	IL*	MCT	G	IL*	MCT
Day 0	52(7)	47(5)	41(6)	43(12)	37(7)	34(11)	46(12)	64(7)	55(3)
Day 7	42(7)	41(6)	28(6)	32(10)	24(4)	44(17)	53(7)	39(5)	59(7)

Values are mean (s.e.m.). * $P<0{\cdot}05$

NK activity was unaffected by TPN in all groups. However, LAK cell generation was suppressed after 7 days of TPN with IL ($P<0{\cdot}05$) but by neither of the other regimens.

Since lipid is an important component of TPN, we suggest that MCT should be the regimen of choice for immunocompromised patients.

1. Monson JRT, Sedman PC, Ramsden CW, Brennan TG, Guillou PJ. Total parenteral nutrition adversely influenced tumour-directed cellular cytotoxic responses in patients with gastrointestinal cancer. *Eur J Surg Oncol* 1988; **14**: 435–43.

Glutamine-enhanced enteral diets in stressed dogs improves nitrogen balance without increasing portal ammonia

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During stress the jejunum is important in metabolizing glutamine to maintain mucosal integrity and release metabolites into the portal blood supporting hepatic protein production and gluconeogenesis. Few commercial feeds contain glutamine, therefore endogenous sources are broken down to maintain the jejunal requirement, leading to an increased negative nitrogen balance. Ammonia production by jejunal enterocytes during glutamine metabolism has prevented glutamine inclusion in standard feeds. To assess the effect of glutamine-enhanced enteral diets in the stress response on nitrogen balance and portal ammonia production the following experiment was carried out.

Groups of standard beagle dogs were stressed by a laparotomy with either an enterotomy (E) or 60 per cent enterectomy (T). These two groups received either a glutamine-free diet (C) or 30 per cent glutamine-enhanced diet (D). The diets were isocaloric and isonitrogenous. Daily nitrogen balance was calculated over 72 h and portal blood sampled for ammonia levels. The results are shown in the *Table*.

	Cumulative nitrogen balance (g/day)		
Group	Day 1	Day 2	Day 3
EC ($n=7$)	0·53 (0·82)	−0·37 (1·48)	−3·70 (3·38)
ED ($n=6$)	2·16 (1·27)	3·09 (1·76)	4·61 (0·99)*
TC ($n=5$)	1·25 (1·25)	0·68 (2·34)	−1·60 (6·63)
TD ($n=6$)	2·36 (1·05)	−0·09 (4·69)	−5·07 (2·79)

		Portal ammonia (mmol/l)					
	Fasting	1 h	6 h	18 h	24 h	48 h	72 h
EC	212(43)	252(50)	232(105)	237(13)	294(161)	169(120)	144(111)
ED	142(44)	181(66)	205(44)	166(96)	160(86)	124(69)	142(35)
TC	203(47)	216(61)	191(48)	190(68)	188(54)	154(45)	155(87)
TD	157(68)	225(59)	254(77)	267(111)	227(54)	181(137)	227(101)

Values are mean(s.d.) * $P<0{\cdot}005$, ANOVA

Glutamine-enhanced enteral diets improved nitrogen balance in stressed dogs without increasing ammonia release. Stressed patients may benefit from supplementary glutamine.

Improved respiratory muscle function after a short course of intravenous nutrition

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Protein depletion is a risk factor for postoperative pneumonia[1]. We assessed the effect of 14 days of preoperative intravenous nutrition (IVN) on respiratory muscle function. Nineteen patients (10 men, mean(s.d.) age 30 (12) years) who had lost 35 per cent of their protein stores associated with a 25–40 per cent level of respiratory functional impairment had repeated measurements of total body protein (TBP) by neutron activation analysis with measurements of respiratory muscle strength (RMS) and forced expiratory volume (FEV_1) All results were compared with a control group (10 men mean(s.d.) age 34 (9) years).

This short course of IVN increased visceral proteins but not TBP However there was a 5–15 per cent increase in respiratory function, which was maximal at 4 days This improvement is significant when compared with a total gain of only 10–25 per cent measured 200 days later after an 11 per cent gain in protein stores.

		Patients			
	Controls	Day 0	Day 7	Day 14	Day 200
TPB (kg)	11·3(0·6)	7·3(0·5)**	7·4(0·5)*	7·5(0·5)*	8·6(0·4)**(**)
RMS (cmH_2O)	104 (10)	65 (8)**	76 (9)§	78 (10)*	90 (9)†(†)
FEV_1 (litres)	4·0(0·3)	3·0(0·2)**	3·2(0·2)§	3·3(0·2)*	3·4(0·2)*(‡)

Values are mean(s.e.m.). TBP, total body protein; RMS, respiratory muscle strength; FEV_1, forced expiratory volume. Difference from previous measurement (final difference from control values). * n.s., † $P<0{\cdot}05$, § $P<0{\cdot}005$, ** $P<0{\cdot}0005$, Student's paired t test

These data suggest that depleted patients awaiting major surgery may benefit from 4–7 days IVN.

1. Windor JA, Hill GL. Risk factors for postoperative pneumonia *Ann Surg* 1988; **208**: 209–14.

Effects of supplemental arginine on wound healing

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Protein calorie malnutrition (PCM) impairs normal wound healing. Full nutritional repletion can restore healing to normal, but specific substrates may suffice. The aim of this study was to determine if the anabolic amino acid arginine (Arg)[1] could limit the adverse effects of PCM on wound healing. Adult male Fisher rats (250–300 g; $n=96$) were randomized to receive a 24 per cent or 2·5 per cent protein diet for 14 days before wounding with an 8 cm dorsal cutaneous incision After wounding, rats were randomized to continue on their existing diet or to receive 1 per cent Arg or isonitrogenous 1·7 per cent glycine (Gly) supplementation in addition to their existing diet. On days 14 and 21 after wounding, eight rats in each group were killed and 6 cm skin strips (five/rat) perpendicular to the wound axis were tested for wound bursting strength (WBS) using an MTS dynamic material tensiometer. The results are shown in the *Table*

Group		Wt change (g/day)		WBS (N)	
Before wounding	After wounding	Day 14	Day 21	Day 14	Day 21
24%	24%	1·3(4)	0·9(5)	16(4)	29(8)
24%	+Gly	1·3(0·5)	0·8(0·4)	16(5)	27(5)
24%	+Arg	1·4(0·2)	1·1(0·5)	17(5)	31(7)
2·5%	2·5%	−1·5(0·4)	−0·9(0·4)	13(1)	18(1)
2·5%	+Gly	−1·2(0·3)	−0·7(0·5)	13(2)	21(2)
2·5%	+Arg	−1·4(0·2)	−0·5(0·5)	15(3)	26(3)*

Values are mean(s.e.m.). *$P=0{\cdot}008$ Arg *versus* 2·5 per cent +Gly; $P<0{\cdot}001$ Arg *versus* 2·5 per cent

Supplementay dietary Arg significantly increased WBS at day 21 in protein-malnourished rats compared with both Gly and non-supplemented groups. These data suggest that Arg may have a role in the management of malnourished surgical patients at risk of wound failure.

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Effect of fibrin glue on the mechanical properties of healing wounds

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Fibrin-based glues have a wide range of uses in surgical practice. Currently available commercial fibrin glues are not guaranteed to be free of viral particles and have varying concentrations of fibrinogen, thrombin and factor XIII In developing a safe fibrin glue, various formulations with differing fibrinogen, thrombin and factor XIII concentrations were tested on the healing of full thickness skin incisions in male Wistar rats closed with tape alone, or tape and glue.

Rats were killed at 4 and 8 days, wounds were excised and frozen at −70°C until testing. After thawing, multiple strips from the wounds were tested to rupture on an Instron tensiometer and stress and elastic modulus measured. The results showed that for a fibrinogen concentration of 39 g/l, wounds at 8 days had significantly higher mean(s.d.) stress values (52(10) g/mm^2) compared with control wounds (35(8) g/mm^2). However for a fibrinogen concentration of 58 g/l wounds were significantly weaker (26(10) g/mm^2) than controls The same pattern was seen with varying thrombin concentrations. A thrombin level of 200–600 units/ml gave significantly stronger wounds than both control wounds and wounds with a thrombin concentration of 1000 units/ml. These latter wounds in turn were weaker than control wounds. Similar experimens with factor XIII indicate that no additional factor XIII (on top of the native factor XIII already present) is necessary for adequate glue function Added factor XIII does not function in the same way as native factor XIII of a similar concentration.

We conclude that formulation of fibrin glue must be carefully performed as so to enhance and not inhibit wound healing.

Increased morbidity with abnormal pulmonary albumin flux in septic adult respiratory distress syndrome

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Damage to the pulmonary capillary membrane can be elicited by a rising lung:heart ratio (expressed as Slope Index (SI × 10^{-3} min^{-1})) of intravenous ^{99m}technetium-labelled albumin measured with a γ camera. Thirty patients with septic adult respiratory distress syndrome (ARDS), 13 patients with congestive heart failure (CHF) and 32 controls (C) underwent comparative scintigraphic studies A sepsis score was calculated for ARDS patients. There was no significant difference between SI in the control (mean(s.d.). 0·14(0·4)) and CHF (mean(s.d): 0·25(0·8)) groups The ARDS patients had a higher ($P<0{\cdot}001$) SI (mean(s.d.): 0·89(0·5)) than either the control or CHF groups. In the ARDS group, 15 patients had a normal and 15 an abnormal SI. There were no differences in gas exchange parameters or mortality between ARDS patients with normal or abnormal SI Patients with abnormal SI required longer ($P<0{\cdot}01$) mechanical ventilation and hospitalization, spent longer in the intensive care unit (ICU) and had higher ($P<0{\cdot}05$) mean sepsis scores than patients with normal SI (see *Table*).

	Ventilator (days)	ICU (days)	Hospital (days)	Sepsis score
Normal SI	7 (1)	11 (1)	35 (5)	13·3 (1·2)
Abnormal SI	36 (5)*	67 (9)*	113 (20)*	19·6 (1·4)**

Values are mean(s d.). * $P<0{\cdot}01$, ** $P<0{\cdot}05$ abnormal *versus* normal SI

This technique successfully differentiated permeability from non-permeability oedema and predicted increased morbidity in a subgroup of septic ARDS patients with increased pulmonary capillary albumin flux.

Correspondence

Management of ingrowing toenail

Sir

I was surprised that the leading article by Murray (*Br J Surg* 1989; **76**: 883–4) did not mention 'soft tissue' operations for ingrowing toenail. The opinion that the skin rather than the nail is at fault is supported by evidence that the shape of the nail does not differ from that in age matched controls[1], both groups showing considerable variation in nail curvature and axis deviation. As the nail does not appear to be abnormal, operations have been devised to treat the soft tissue abnormality, aiming to give a better cosmetic and functional result.

Radical excision of the nailfold, as described by Antrum[2], gave an 80 per cent cure rate. Subsequently, in a controlled trial, it produced only two recurrences in 32 treated toes[3]. This operation is quick and simple to perform, and does not disturb the nail or nail bed. It is very suitable for use by junior surgical trainees, to whom toenail surgery is often delegated. Its only disadvantage is that full healing takes an average of 5 weeks. The cosmetic result is excellent – indistinguishable from a normal toe.

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Pelviureteric junction obstruction

Sir

We read with interest the paper by H. C. Ward and R. J. Brereton (*Br J Surg* 1989; **76**: 818–9) and would agree with their advice concerning the diagnostic use of ultrasound or intravenous urography. It should be stressed, however, that in this group of children the pelviureteric junction obstruction is intermittent and therefore demonstration of a hydronephrosis without a dilated ureter is most likely during an attack of pain. In practice many such children are under out-patient review and may come to investigation during periods of well being. In order not to miss the diagnosis in these children we would recommend requesting an ultrasound or intravenous urogram with a diuretic challenge.

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Aids to the diagnosis of acute appendicitis

Sir

The diligent review by Hoffmann and Rasmussen (*Br J Surg* 1989; **76**: 774–9) of a difficult clinical area (where opinion has often substituted for observed fact) is warmly to be welcomed.

Whilst we are not qualified to discuss all diagnostic modalities from extensive first-hand experience, as regards computer-aided decision support the comments seem to us both fair and well-founded. For example, as regards cost we have long argued it makes little sense to acquire a large expensive computer solely for decision support, despite resultant savings. (Fortunately nowadays, this is not necessary; most units have a small personal computer or access to a patient administration system)

Perhaps we may be permitted one or two further comments, first concerning computer accuracy. It is correct to say 90 per cent is achievable – several centres have attained this figure, not just in the UK[1,2]. However, although all modalities are to some extent operator-dependent, the computer is alone in relying on data provided by the doctor. Provided with incomplete or ineptly-elicited clinical data, the computer's accuracy may be no greater than that of the unaided clinician.

The corollary of this point is crucial. As the computer is dependent upon clinical data, its presence acts both as a stimulus towards 'doing it right' and as a valuable training aid for young inexperienced surgeons, whose own performance improves to match that of the computer's[3] In this it stands alone amongst the 'investigative' modalities

Thus the ultimate place of computer prediction may not be as an isolated investigation but as an educational tool and a prelude to selecting, in appropriate cases, more expensive and more invasive investigations. Readers may be interested to know the European Community has recently launched a 'concerted action' involving 10 000 patients (in over 50 EC hospitals) to explore further this important topic. Nevertheless, the review's central theme is important and, on the available evidence, correct. In the age where several effective modalities are available, the old yardsticks no longer apply. A negative appendicectomy rate of 30 per cent (still prevalent in many centres) is no longer necessary and no longer acceptable In this day and age (where audit is *de rigeur*) it behoves all surgeons to check their own unit performance figures Where these are outwith (now) acceptable values, (and rates below 20 per cent are now readily and reproducibly attainable[3]) surgeons should clearly take action, but starting, we suggest, with insistence upon the highest standards of patient interview and physical examination.

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Stapled ileal J pouch–anal anastomosis

Sir

We would like to reply to the letter from W. A Kmiot, K Hosie and M. R. B Keighley (*Br J Surg* 1989; **76**: 989) We described a technique of ileoanal pouch construction which involves eversion of the lower rectum to place the distal purse-string for the anal anastomosis (*Br J Surg* 1989; **76**: 350–1). Your correspondents are worried that this technique may lead to incontinence.

We would point out that when the rectum is fully mobilized down to the pelvic floor it can be everted without even minor dilatation of the anal canal. It should be emphasized that meticulous and obsessive dissection of the rectum is absolutely essential. With this method we have found that the postoperative resting and squeeze pressures of the anal musculature show no change from the values obtained before the operation. Although we understand the reservations expressed in the letter, in practice, even minor incontinence has not been a problem in the patients treated by this technique.

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Biliary anatomy

Sir

It is always mildly flattering to have one's own work quoted and it was kind of McQuillan *et al.* (*Br J Surg* 1989; **76**: 696–8) to refer to our paper on biliary anatomy[1]. It is, however, extremely irritating to be misrepresented. Page and I did not specifically refer to the subvesical duct of Luschka though we did describe cholecystohepatic ducts. We most certainly did *not* advocate attempting to repair ducts of this minute size. Indeed it would be a fatuous *tour de force* of technical expertise to even try to do so! I have previously indicated in correspondence with the Journal that such fine filamentous ducts are not infrequently unrecognized at the time of cholecystectomy. Many may well be diathermied or suture ligated and in those few which are unrecognized, and which drain for a while after operation, no harm seems to come to the patient. The more substantial accessory hepatic ducts need recognizing at operation and must be carefully avoided.

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1 Benson EA, Page RE. A practical reappraisal of the anatomy of the extrahepatic bile ducts and arteries. *Br J Surg* 1976; **63**: 853–60.

Benign non-traumatic inflammatory strictures of the extrahepatic biliary system

Sir

We were interested to read the paper by Standfield *et al* (*Br J Surg* 1989; **76**: 849–52) on benign extrahepatic strictures without characteristic features of sclerosing cholangitis. The authors may have overlooked our paper[1] describing six patients with a similar condition which we christened 'proliferative cholangitis' because of the predominant histological feature of intramural bile duct proliferation, the radiological appearances of which may be diagnostic. Standfield *et al.* noted similar epithelial changes although they may not have been as remarkable. They saw chronic inflammation and ulceration in almost all patients and such features were also noted in some of ours. We may both have described the same or a very similar condition with a spectrum of histological abnormality and we doubt whether it is as uncommon as the scarcity of reports suggests.

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Book reviews

Current Gastroenterology. Volume 8

G. Gitnick. 233 × 160 mm. Pp. 431. 1988 Illustrated. Chicago· Year Book Medical Publications. £53.50.

In the preface of this volume it is suggested that the 12 chapters are all written by experts in their field. With the exception of two chapters from Bologna the remaining experts are all North American. The text is written in the American rather than in the English language, e g. gastroenterologic The chapters vary in size and approach; some are written like a standard text book clearly representing the didactic views of an experienced clinician whereas others are reviews with brief comments on many topics and usually accompanied by vast numbers of references.

The chapter on endoscopy is well written and enjoyable, particularly the author's view of the future. The section on percutaneous endoscopic gastrostomy made interesting reading. In the large chapter on small bowel disease the North American experience in patients suffering from AIDS is well documented. The chapter on the colon is very much in keeping with British opinions although there was a startling statement that: '... current guidelines suggest that all patients over 35 years should have yearly haemoccult tests and 3-yearly flexible sigmoidoscopy'; the logistical and financial implications of that statement would have major consequences In the chapter on the pancreas there is an excellent section on the vexatious problem of idiopathic acute pancreatitis.

The topic of when to operate in patients with acute necrotizing pancreatitis is discussed but the three papers quoted are dated. The remaining chapters are devoted to the oesophagus, stomach, gastrointestinal hormones, gastrointestinal cancer, nutritional aspects of gastroenterology, imaging of the abdomen and two verbose chapters on inflammatory bowel disease which could have readily been condensed into a single chapter.

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Gastroesophageal Reflux

G Jamieson, A Duranceau. 230 × 160 mm. Pp 281. Illustrated. 1988 Philadelphia. W. B. Saunders. £31.00

This book is a joint production from Montreal and Adelaide and all contributors bar one are surgeons It is extremely well produced and I found the chapters on diagnostic aspects of gastro-oesophageal reflux particularly helpful. A logical scheme is proposed taking into account the large number of ways of documenting gastro-oesophageal reflux ending up with 24 h ambulatory pH monitoring. It is a particularly valuable source of references on each topic and includes some excellent historical references going back for instance to the observations of Quincke in 1879 and Hertz in 1910 on the pathogenesis of gastro-oesophageal reflux disease.

Some of the rather confusing aspects of reflux disease such as the association with globus and the mythical Schatzki ring are fully and comprehensively discussed Needless to say there will be deficiencies in any book and I thought the Nissen fundoplication was rather lightly described given the fact that it is the world-wide standard antireflux operation. At the end of this section on antireflux surgery I was unclear what the Editors thought was the correct way of performing this operation or even what they thought were the important variables in determining success. The book, however, remains a useful guide to the understanding of gastro-oesophageal reflux and I would recommend it particularly to surgeons who deal with this disease and especially for those who have a research interest in it.

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Biliary Lithotripsy

J. T. Ferrucci, M. Delius, H. J. Burhenne. 260 × 185 mm. Pp. 309 Illustrated. 1989. London· Wolfe Medical Publications. £61 00.

Cholecystectomy is at present being assailed by 'non-invasive' procedures for gallstone clearance, such as, extracorporeal lithotripsy and dissolution therapy, as well as 'minimally invasive' methods, including percutaneous stone dissolution or mechanical extraction. This book does not stay within the confines of its title but reviews all these latest techniques. It is a distillate of the first International Symposium on Biliary Lithotripsy, held in July 1988

The book gives a good overview of the subject as it was in July 1988. It starts with a discussion of the science behind shockwaves, the action of different lithotripters and their effects on gallstones and soft tissues. Next, there are a number of reports from various authors, giving their experiences with extracorporeal lithotripsy. These vary from the wide experience of the pioneering Munich group to those with much less experience. Further subjects tackled include sections on the natural history of gallstones, their dissolution and the prevention of recurrence. Some experience using lithotripsy for bile duct stones is given, while the section assessing the technology, the market, and the future has a distinct North American flavour Finally, there are presentations by seven manufacturers of extracorporeal lithotripters describing the specifications of their machines. This section might be helpful for prospective buyers, although the best type of lithotripter for gallstones remains undecided.

For those who wish to embark on this form of therapy, this book, which is well produced, would be very useful If, however, your interest is more casual, then it may be cheaper to obtain reprints of about half a dozen seminal papers on the subject.

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Year Book of Surgery 1988

S. I. Schwartz, O. Jonasson, E. Peacock, G. Shires, F. Spencer, J Thompson. 235 × 255 mm. Pp. 483 Illustrated 1988. Chicago. Year Book Medical Publishers Inc £38.00

The Year Book of Surgery is one of a series of over three dozen volumes published each year to cover the whole field of medicine. The volume on surgery has 27 chapters covering a wide spectrum of general surgery but including trauma, burns, transplants and cardiac surgery. Each chapter consists of some two dozen abstracted papers considered by the editors to be the most interesting or significant publications of the year 1987. Each abstracted paper is then followed by editorial comment which I find by far the most interesting feature of the book. The editors are American and have consulted 70 journals to make their selection. There is a fair balance between publications on each side of the Atlantic. This is a book for the post fellowship reader as there is rather more emphasis on rare but challenging surgical problems, such as medullary carcinoma of thyroid and pylorus preserving pancreatoduodenectomy, papers on everyday problems of hernias, piles, and varicose veins were not reviewed. Were there no significant contributions in 1987?

At the beginning is an annual overview where the contents of each chapter are skilfully summarized. As we all now have to specialize it is useful to have this overview of what is happening outside our own fields. At the end there is a good subject and author index. Is this a book for the general surgeon who just cannot keep up with journals? Yes and no. It certainly drew my attention to good articles that I should not have overlooked in British journals but the choice of papers reviewed is so personal to individual sub-editors that there cannot be comprehensive coverage. Dr Schwartz and his team have put in a massive amount of work to produce the volume and time will not be wasted reading sections of the book, but it is one for the library rather than personal bookshelves.

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Scientific Foundation of Surgery. 4th ed.

J. Kyle, L. C. Carey. 285 × 215 mm. Pp. 651. Illustrated. 1989. London: Heineman Medical Books. £75.00.

Shortly after his retirement from the Chair of Surgery in Liverpool in 1963, Charles Wells conceived the idea of providing surgeons, both trainee and established, with a comprehensive text describing the scientific and physiological basis of surgery. That such a book was long needed was undoubted and, with his colleague, James Kyle, he produced the eminently successful first edition of Scientific Foundations of Surgery. In addition, Charles Wells had identified a yawning gap in the clinical literature, because it became quickly evident that many other clinical disciplines also lacked an appropriate monograph on the scientific basis of their discipline. As a result, an entire series of scientific foundation books were published over the succeeding years.

This fourth edition, published in the year in which Professor Wells died, brings the surgeon up-to-date with scientific advances in surgery at the end of the 1980s. The success of this book is assured by the continuing editorship of James Kyle of Aberdeen who has been joined by Dr Larry Carey of Columbus, Ohio. The value of the book lies not only in the clear exposition of the basic sciences of surgery, but also the ability of the Editors to ensure that the contributors identified and described the clinical relevance of surgical physiology and pathophysiology. In 59 chapters, the 85 contributors have revised or rewritten much of the text. Opportunity has been taken to include many recent developments. Many chapters are excellent: the new chapter on imaging is a model of its kind.

Not surprisingly in a book of this size there is some unevenness of treatment and a need for stricter editorial control. For example, there has been recently considerable interest in anorectal function and the clinical measurements which are necessary in patients with distressing faecal incontinence. The writer of this chapter should have been given more space to discuss the mechanisms of faecal continence and to describe the methods currently used for its diagnosis and treatment. The entire complex problem of portal hypertension and bleeding oesophageal varices is ignored, the only reference to the portal vein being contained in one short paragraph in an anatomical section in the chapter on the pancreas. I could find no reference to the pathophysiology of oedema or ascites, nor to the mode of action of modern diuretics which play an important part in the care of the critically ill. Nevertheless, the chapter on shock syndrome and intensive care and acute renal failure should be required reading of all surgical trainees.

Almost 20 years after the launch of the first edition, this book will, during the 1990s, meet the requirements of surgical trainees taking examinations in the UK. The new regulations for the Fellowship of the Royal Colleges relate the basic sciences to clinical surgery very much more closely than hitherto. Charles Wells was a strong protagonist of a close linking of examinations in the basic sciences with those in surgery in general; indeed the book had been launched with that end in view. At last events are catching up with his prescience and, without doubt, this book and its successive editions will become the classic text for the young surgeon.

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Kidney Transplantation, Principles and Practice. 3rd ed.

P J Morris. 235 × 155 mm. Pp. 788 Illustrated. 1988. Philadelphia. W B Saunders. £56.50.

Renal transplantation is now firmly established as the optimal treatment for the vast majority of patients with end-stage renal failure. This book is aimed at all of those involved in the care of patients undergoing renal transplantation – an objective which the two previous editions have achieved with great success as shown by their international popularity. In this new edition, Professor Morris has drawn together contributions from physicians, surgeons and scientists based in North America, Europe and Australasia. Most of the chapters from the previous edition have been extensively revised, updated, and in many cases completely rewritten and several new chapters have been added. The result is an expanded edition which comprehensively covers all aspects of renal transplantation, both established and new Despite the large number of contributing authors, the 30 chapters which make up this edition are well integrated and of even quality The book is uniformly well illustrated and all chapters are extensively referenced, for example the chapter on Cyclosporine contains well over 200 references.

Progress in renal transplantation has been based largely on scientific discovery rather than technical advances and this is reflected in the content of many of the chapters. For example, there are excellent reviews on the immunology of graft rejection, the experimental background to specific unresponsiveness, HLA matching and crossmatching and on aspects of renal preservation before transplantation. At a clinical level, the medical and surgical aspects of dialysis and transplantation are all covered, including a thorough description of transplantation in children. The surgical techniques of vascular access and renal transplantation are clearly outlined and the evaluation of the living related and the cadaver kidney donor is discussed together with the operation of donor nephrectomy. Also included is an update on technical aspects of the increasingly common practice of harvesting kidneys from multiorgan cadaveric donors.

Graft rejection remains the major problem following renal transplantation and a notable feature of this new edition is the increased coverage given to immunosuppression – six chapters in all. Together, these describe current views on this crucial and often controversial area. There are also informative chapters on the prevention and management of the other complications which may occur after transplantation, including technical, infective and cardiovascular problems The editor has identified and included several new chapters of particular relevance to contemporary practice. For example, the diabetic with renal failure, and renal transplantation in the developing world are each addressed with the special problems which may be encountered in these two situations highlighted. In the final chapter, the editor reviews the overall results of renal transplantation in the management of end-stage renal failure. The improvement in graft survival continues and the current results of transplantation are now very good. Nevertheless, as pointed out, there is no room for complacency and, in particular, there is still considerable scope for improving the long term prospects of patients after transplantation Hopefully, with the current pace of discovery it may not be too long before the scientific advances presently taking place are translated into clinical practice.

This new edition of 'Kidney Transplantation' will ensure its continued position as the outstanding single volume on renal transplantation and as such it is unrivalled and therefore highly recommended for anyone who is involved in the care of patients undergoing renal transplantation.

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Concise System of Orthopaedics and Fractures

A Graham Apley, L. Solomon. 235 × 165 mm. Pp. 300. Illustrated. 1988. London Butterworths. £14.95.

This book is an offshoot of the larger Apley's system of orthopaedics and fractures which has been a standard and extremely popular text book of orthopaedics since it was first published in 1959. To a large extent the format of general orthopaedics, regional orthopaedics, fractures and joint injuries follows the original text book The feel of the book is generally the same as its larger predecessor and many of the excellent diagrams are repeated The text has however been completely rewritten and certainly achieves its aim of expanding the principles of the subject. The book is therefore aimed at undergraduate students and junior doctors together with those important members of the allied professions. Although concise it is not a short book with some 330 pages in all and despite its paper cover is still too heavy to carry in a medical coat. The book like its predecessor is beautifully styled and I am sure will rapidly gain affection with the readership to whom it is aimed. I would be disappointed, however, if it were to supercede the System of Orthopaedics and Fractures which has for so long been a stalwart of British postgraduate orthopaedic training.

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Vascular Birthmarks. Hemangiomas and Malformations

J. B. Mulliken, A. E Young. 265 × 190 mm. Pp. 483. Illustrated. 1988. Philadelphia: W. B. Saunders. £98.00.

This beautifully produced and well illustrated volume has been edited and written by two surgeons, as they themselves put it; 'one from Old England and one from New England'. The book is written with the New English spelling and has multiple contributors Four major sections make up the volume. The first section consists of a chapter on 'Vascular Birthmarks in Folklore, History, Art and Literature' which is both informative and entertaining and includes many illustrations of individuals who have some connection with vascular birthmarks These individuals range from Cicero who apparently had a vascular anomaly below his left eye, to the present day General Secretary of the Soviet Union. There follows an article by John Mulliken on the classification of vascular birthmarks. This area is controversial and the literature surrounding it is very confusing. Problems in classification are fully discussed and the author of this chapter finally recommends a separation of vascular birthmarks into hemangiomas (commonly not present at birth) and vascular malformations ('by definition' present at birth). It is stated however that 'arteriovenous anomalies' can first appear later in childhood and the early adult period and it is unclear as to whether the authors regard these as hemangiomas or malformations.

The arrangement of the following sections of the book follows the separation into hemangiomas and malformations, and pathogenesis, diagnosis and treatment are considered. The final section of the book is entitled 'Problems and Solutions' and includes articles on regional vascular malformations and assorted other contributions including chapters on the therapeutic techniques of laser therapy and embolization and a final chapter on the emotional impact of a vascular birthmark. In the preface the authors state that the stimulus to write this book was a series of meetings of the International Workshop for the study of Vascular Anomalies. The overall structure of the book rather reflects this and although there has obviously been some careful editing there is still some degree of overlap between the various chapters. Despite this and occasional errors (a glomus tumour is referred to as a hemangiopericytoma, and generalized essential telangiectasia is given as a synonym for angioma serpiginosum), there is much useful new and beautifully illustrated material present in this volume in addition to a well referenced and up-to-date bibliography. The authors intend their book to be a reference for both primary and secondary care physicians and surgeons. 'Vascular Birthmarks' can be warmly recommended not only to these groups but to anyone with an interest in this common and fascinating group of conditions.

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An Illustrated Guide to Gastrointestinal Motility

D. Kumar, S Gustavsson. 255 × 195 mm. Pp. 470. Illustrated. 1988. Chichester John Wiley and Sons £65.00

Gastrointestinal motility was once the Cinderella of clinical science, rarely represented in general surgical and gastroenterological endeavour. At the upper end of the gastrointestinal tract the dominant interest was in peptic ulcer, and the effects of acid and pepsin in the stomach and oesophagus carried much more weight with surgeons Distally there had always been a small group interested in the problem of diverticular disease and related motility problems, but the part in between, the entire mid-gut area, was more or less inaccessible before the advent of 30 years of telemetering capsules At first the use of these was difficult and the results somewhat uncertain but with time more reliable techniques have evolved and taped records make possible longer study periods. With the gradual disappearance of peptic ulcer as a surgical disease there is more scope for the surgeon investigating the motor abnormalities of the upper and lower GI tract. Nowhere has this become more apparent than in the colorectal area, all the more so because of the increasing impact of the bowel problems of an ageing population.

The construction of this book is good in content and follows a logical pattern in that it moves from cells and tissues to the motility of normal organs, including sphincters, and then to clinical problems. It includes much about computers in motility assessment and evaluation It has a certain modern attractiveness and is simple and explicit about what can often daunt the novice to this field who may have to use sophisticated apparatus with a day-to-day language different from that in clinical work The methods outlined consider the excitability of cells, the electrical patterns of events and tissues and the means of achieving the pressures which in turn make the end-stage phenomena of such transit happen, and which in turn are studied by radiological and isotope methods as 'organ events' which illuminate function.

To the reviewer the book was a stimulating record of what contemporary knowledge now is in this field. There are magisterial accounts by Christensen, Devroede, Janssen, Vantrappen and Phillips and all the London Hospital contributors who form one-sixth of the entire list of contributions which is surely a great tribute to the growth of gastrointestinal motility science in the Departments of Norman Williams and David Wingate. It can be recommended to all who are interested in this field and is a must for all gastroenterologically-minded surgeons.

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General Thoracic Surgery. 3rd ed.

T. W Shields, 290 × 220 mm. Pp. 1251. Illustrated. 1989 Beckenham Lea and Febiger. £100.00.

The third edition of 'General Thoracic Surgery' weighs-in at 3·65 kg. Dr Shields has succeeded in what must have been a monumental task of coordinating the contributions of 115 authors and although I have not read every one of the 1222 pages of text, there seems little duplication of effort. Each chapter deals with one particular aspect of thoracic disease and is generously illustrated with black and white photographs. The X-ray films chosen to depict particular aspects of chest disease have reproduced well, and my only disappointment was the poor quality of some illustrations of operative details.

As one would expect from such a book, it proceeds in sections from anatomy, physiology and imaging to a systematic review of diseases affecting the various structures of the thoracic cage excluding the heart. The journey takes the reader via diagnostic procedures, pre-, peri- and postoperative management, operative procedures and thoracic trauma Each chapter concludes with references and suggestions for further reading.

Of the sections and chapters I particulary enjoyed reading were those on 'Preanaesthetic evaluation and preparation' and on 'The conduct of anaesthesia' both of which were masterly descriptions of the optimum care for patients undergoing thoracic surgery, and which have important lessons for surgeons and anaesthetists involved not only with thoracic surgery but in the general surgical management of more elderly patients. The paragraph on 'informed consent' struck a sensible balance between providing enough information and unduly alarming the patient, but did make the point that the essence of such discussions should be documented – a lesson we should be adopting much more rigorously for all major surgical procedures. I was also delighted to learn that Dr Fogarty's balloon catheter can be used as a bronchial blocker, being positioned accurately under direct vision with a fiberoptic bronchoscope.

The illustrations in the new chapters on computerized tomography and nuclear magnetic resonance imaging of the thorax reveal very clearly the value of these techniques in clarifying the nature and extent of intrathoracic pathology.

Having spent some time wrestling with inhaled foreign bodies in the past it was salutory to be reminded of the value of careful preparation: 'If 2 h are spent in preparation, the safe endoscopic removal of a foreign body may take only 2 min. But if only 2 min are taken for preparation, the endoscopist may find himself attempting ineffective, makeshift procedures for the next frustrating 2 h' A lesson that applies to many aspects of surgical practice!

Although not a book for every surgeon's bookshelf, medical libraries without a modern text on thoracic surgery can do no better than obtain a copy of this splendid book.

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Liposuction Surgery and Autologous Fat Transplantation

S. Asken. 290 × 210 mm Pp. 166. Illustrated. 1988. East Norwalk Appleton and Lange. £117.70.

It is inevitable that a new surgical technique will find an enthusiast to write a book about it. Liposuction's brief history began with such a disaster in 1929 (the amputation of a leg of a dancer due to a vascular injury) that the next report of its use was not until 1968. By 1982 there were enough interested surgeons to form a Liposuction Society in America. Although the author of this book is a cosmetic surgeon, and most of the indications and results described belong in this category, it does deserve evaluation since it has the potential to fill other needs.

After a chapter on the basic structure and metabolism of fat, which is just acceptable, there is a chapter on the physics of suction which is inadequate. He is on stronger ground describing indications for liposuction and the equipment. He is on less secure ground on the initial consultation and follow-up techniques; having seen the consent form, I can only admire the persistence of the patients who still want to have this procedure done.

As in most plastic and cosmetic surgery books, the series of before and after photographs show attractive results but give little clue to the reliability and reproducibility of these techniques. Clearly this is a technique that needs to be learnt by practical experience which is not readily conveyed on the pages of a book. A major defect is the absence of any critical appraisal of the outcome in the patients who have had either liposuction or autologous fat transplantation, in which section a more critical appraisal of the fate of the transplanted fat would have been welcome. Overall, I am unable to recommend this book as it is insufficiently critical to allow me to be persuaded as to the value of the techniques described, nor is this a subject which lends itself to being learned from a book.

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Lasers in Medicine – An Introductory Guide; 2nd ed.

G. T. Absten, S. N. Joffe. 215 × 135 mm. Pp. 71. Illustrated. 1988. London Chapman and Hall. £7.95.

This small book is an attempt to summarize the use of lasers in medical practice for physicians and surgeons unfamiliar with the effect of laser light on tissue. The book contains introductory chapters on laser physics, the laser–tissue interaction and descriptions of the individual lasers, and finishes with a short chapter on laser safety. The rest of the book contains short descriptions of the uses of lasers in various specialties; there are now 14 of these and the list is still growing. All of these chapters are well-written and accurate; in particular the authors explain the physics well and rightly stress the importance of a good delivery system coupled to the correct laser for a particular application. There are, however, some problems. The whole point of a book on laser applications in medicine is to explain how and why different wavelengths are chosen for different applications, such an explanation is lacking and the reader is left trying to bridge for himself the gap between the physics and the clinical application. Some errors are perpetrated. These include the myth that it is possible to focus light from a Nd-YAG laser within tissue, it is too highly scattered for this. There are also some statements on the use of the Nd-YAG laser in cutting tissue during general surgical operations which are at variance with the literature. There is considerable emphasis on the use of sapphire fibretips with a delivery system for the Nd-YAG laser and such emphasis is misplaced until there is more evidence to show how or indeed whether these devices are an improvement on other delivery systems. The bibliography is very general and somewhat repetitive in nature; a few references to the many definitive review articles which now exist within the specialties would have been helpful. In general this book does give the general reader an introduction to lasers in medicine but further reading will be essential for a proper grasp of the subject.

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Cancer Chemotherapy: An Introduction. 3rd ed.

T J. Priestman. 235 × 155 mm Pp. 209 Illustrated 1989. London Springer–Verlag £19 50.

This is an easy book to read, an excellent introduction to the subject and should be mandatory reading for all surgeons involved in the treatment of cancer patients so that they have a working knowledge of the place of different treatments in the overall management of their patients Dr Priestman gives a very honest approach to the limitations of cancer chemotherapy but at the same time points out its efficacy in those tumours that are sensitive to drug therapy.

Section one opens with an excellent chapter on the 'Principles of tumour growth'. Section two deals only with 'Biological response modifiers' This whole section comprises only six pages. As much work is being undertaken in this field, I would have expected more on this subject. There is little mention of immunotherapy. The chapter on biological response modifiers should have been expanded. Section three on the 'Principles of endocrine therapy' is excellent. The 'Clinical role of chemotherapy' is covered in the last four chapters to varying degrees. Those sensitive tumours are naturally covered more comprehensively. Haematological cancers are covered in much greater detail than solid tumours which are encountered more frequently by surgeons. Dr Priestman has been very direct about the place of drug treatment in solid tumours and the section on 'Carcinoma of the breast' gives a balanced opinion. The use of intraperitoneal chemotherapy and regional perfusion of different organs except limbs has sadly not been covered.

In his chapter on 'The place of chemotherapy in cancer treatment', he points out that unfortunately cancers curable with chemotherapy form only a small proportion, less than 10 per cent, of all malignant tumours, and the older, perhaps less glamorous, modalities of surgery and radiotherapy still account for the greater majority of cancer cures today. I do not think my surgical and radiotherapy colleagues find their treatment of cancer less glamorous, and in fact in my opinion, they are much more so than medical oncology!

I would highly recommend this book for undergraduate students, as it deals with a difficult subject for them crisply and clearly.

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Aids to Postgraduate Surgery

R. M. Watkins, J. M. Thomas. 215 × 135 mm. Pp 300. Not illustrated. 1989. Singapore Churchill Livingstone. £8 95.

'This nuggety book of surgical information. (a) aims to appraise the relative merits of various forms of management; (b) gives recent developments and current controversies, (c) is mainly for the FRCS; (d) is in note format, and is irritatingly verbless.'

The book is clearly popular, is full of useful basic information on selected topics, but falls short of its stated claims. 'Most surgeons prefer to treat hyperthyroidism by surgery' will surprise few, but it is not a serious contribution. The management of bleeding varices contains all the options in various conformations, but has no clear flow of decisions. It leaves out the big message – surgery kills 'C's – and includes a host of interruptions or shunt procedures, mostly of nostalgic interest.

There is a real muddle in oesophageal carcinoma, carefully defined by UICC criteria, then expanded to include obstructing gastric cancers at the cardia. Many series do the same, but .... Surgical options mentioned do not include the common upper partial gastrectomy through the left chest, nor the increasingly popular pull through Alas, there is no mention of the floppy Nissen, nodal dissection in gastric cancer, or medical management of stomal ulcer. The new sections are good, but can one face an examiner (or patient) without a comment on gallstone lithotripsy? I would have liked to see sections on benign breast problems, anal conditions, gynaecological emergencies, day surgery, and audit, rather than Zollinger-Ellison syndrome and radical therapy for carcinoma of the pancreas.

The book is soft-back, useful as a crammer, but not a required library purchase.

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Hernia

L M. Nyhus, R. E. Condon. 260 × 185 mm. Pp. 764 Illustrated. 1989. London. Gower Medical Publishing. £49.50.

Now in its third edition, this book has a well earned place as the standard reference for surgeons interested in any aspect of abdominal wall or diaphragmatic hernias. The text is a delightful mix of anatomy, history and well-balanced didactics from 85 contributors. The first three chapters include a historical survey and a general description of the anatomy of the inguinal region. Contributors writing later chapters on clinical aspects of groin hernia have each given their version of the anatomy, which consolidates the perspective, but sometimes provides an interesting conflict, e.g the exact origins and strength of the iliopubic tract are hotly debated. Nevertheless, several authors admit there is a spectrum of structural variation to be found in the groin of patients with hernias; consequently repair should be tailored to take account of the structures present. Wantz writing about the 'Canadian repair' (Shouldice technique) believes that all inguinal hernias can be repaired by a single method, except indirect hernias in young patients and repeated recurrences.

Prosthetic materials are given a good airing, so much so that in the preface the Editors caution against the wave of enthusiasm which is currently sweeping the surgical world regarding its use in hernia problems. Nevertheless, Condon states that he inserts a prosthesis to reinforce a hiatal hernia repair in every instance. Certainly many surgeons may feel that the natural tissues are adequate for use in antireflux procedures. A technique that has not found popularity amongst British surgeons, the pre-peritoneal approach, is described in three sections with an enlightening and well-illustrated contribution by Stoppa. As a reference text the surgeon will not find a better book to refer to if he wishes to discover more about such rare hernias as Richters and Littres, Spigelian hernia, supravesical or sciatic hernia and many others. Several chapters are devoted to diaphragmatic hernia and reflux peptic oesophagitis with authoritative contributions from Hill, Orringer, DeMeester and others. The standard layout in each section is a historical over-view, with some discussion of the anatomy and outcome for the technique described. The result is a very authorative and well balanced treatment of the subject which will enable the surgeon to refer to the text for help in handling even the most difficult hernia in adults or in children. Finally, there is a short, but helpful section on medico legal aspects of hernia which applies to American law, but has an important message for all in our current climate of escalating litigation. The so called 'compensable' hernia sustained while working, and the subject of ischaemic orchitis resulting from herniorrhaphy of the groin are well discussed. Inevitably, one can find a few blemishes in this otherwise excellent book, and to me these were the outdated and rather unclear line drawings in a few chapters, the puzzling absence of a member of the Shouldice Clinic to contribute the chapter on the 'Canadian repair', the failure to discuss the work of Jenkinson apropos incisional hernia, and the largely obsolete descriptions of repair of sliding inguinal hernias by reperitonealization.

This book can be highly recommended as a comprehensive operative manual, a reference book and a historical survey of hernia repair this century. For these reasons the third edition will become the standard work for hernia surgeons.

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Gray's Anatomy. 37th ed.

P. L. Williams, R. Warwick, M. Dyson, L. H. Bannister. 305 × 235 mm. Pp 1598. Illustrated. 1989. Edinburgh: Churchill Livingstone. £70.00.

Gray's Anatomy must be internationally the best known text book in the whole field of Medicine. This year we see the 37th edition (appearing only 9 years after the 36th) in its 131 years of distinguished existence: this, in spite of terrible book reviews of the 1st edition in *The Lancet* and in the *British Medical Journal*! The present Gray is very different in its format, size and much of its content to the war time edition that myself and my contemporaries cut our anatomical teeth upon. It is, of course, now so large and heavy that it can for the most part be regarded only as a book of reference. I use it to obtain the ultimate truth when my students argue with me about terminology or when an unresolved problem crops up in the dissecting room – and under these circumstances it never lets me down. The modern Gray proves that anatomy is not as dry as dust but is a living subject. There are magnificently illustrated sections on evolution, cellular anatomy and embryology. However, the bulk of Gray remains the detailed mapping of the human body. But here, in addition to conventional excellent illustrations of macroscopic topographical anatomy, together with its authoritative text, there is also complementary radiology, computerized tomography, conventional histology and electron microscopy.

At the extremely cheap price of £70 00, representing about five pence a page, today's Gray's Anatomy can only be described as the medical bargain of the year.

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Common Problems in Gastrointestinal Surgery

J. Fischer. 240 × 155 mm Pp. 451. Illustrated 1989. Chicago Year Book Medical Inc. £36.00

This book is part of the series 'Common Problems in Surgery' edited by Richard F. Kempczinski and consists of 58 chapters each devoted to a defined clinical problem. Surprisingly the remit of gastrointestinal surgery includes chapters on problems of the breast, thymus, lung and thyroid gland.

The concept of this series is to present the personal views of distinguished surgeons on a specific clinical problem with an emphasis on practical surgical management. In general the 58 authors (all from North America except two from the UK) succeed in this task aided by occasional interjections by the Editor As a result a reader can, in 10–15 min, obtain a specialized and authoritative opinion on the practical management of a particular problem

In practice each author usually manages to give a good overview of the clinical subject so that unconventional views are easily placed in perspective. There are six main sections in the book. The sections on the upper gastrointestinal tract and trauma are probably the most interesting whilst the section on small and large intestine is probably of less interest. It is a book best read in short sections and should be enjoyed by surgeons of all grades. It is best kept on a surgical ward

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Renal Transplantation. 1st ed.

E. L. Milford 235 × 155 mm. Pp 293 Illustrated 1989. Churchill Livingstone. £50.00

This is a curious book. It is American, which does not help in making it readable and relevant, but that is not the problem. It is one of a series, entitled 'Contemporary Issues in Nephrology', and the Preface indicates that it is written for and by clinicians – including nephrologists, urologists and transplantation specialists. Yet its content is strangely removed from clinical practice. There is the paradox that the book tells you exactly how many microlitres of rabbit serum to use in the cytotoxic cross match before transplantation, but not how many milligrams of cyclosporin to give the patient afterwards. There is very little surgical detail, yet the chapter on surgical complications tells you how to approach and manage a transplant renal artery stenosis but not how to avoid it.

The book does contain much information, with many chapters comprehensively referenced (although already slightly out of date) and there is great detail in the chapters describing the immunological background to transplantation and the immune response. Somehow it does not hang together in a particularly well organized way and the overall book is considerably less useful than the sum of its parts It is not a major reference book, but many of the chapters would nonetheless make worthwhile reading for surgeons interested in renal transplantation

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Notices and announcements

10–15 December 1989
Osteoarthritis of the knee, aetiology, management and recent advances
London, UK
Information: The British Council Courses Dept, 65 Davies Street, London W1Y 2AA

10–12 January 1990
Surgical Research Society Meeting
Liverpool, UK
Information: Mr C. R Mackie, Dept of Surgery, University of Liverpool, PO Box 147, Liverpool, L69 3BX, UK

17–22 January 1990
Introduction to Endocrine Investigations
Newport Beach, California, USA
Information: Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

19–21 January 1990
26th Head and Neck Course
Liverpool, UK
Information: Professor P. M. Stell, Dept of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX, UK

20–21 January 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

28 January–8 February 1990
The Biological Basis of Radiotherapy
London, UK
Information: The British Council, Courses Dept, 65 Davies Street, London W1Y 2AA

4–9 February 1990
HIV and AIDS: Management and Control
London, UK
Information: The British Council, Courses Dept, 65 Davies Street, London W1Y 2AA

4–10 March 1990
Cancer in Children
London, UK
Information: The British Council, Courses Department, 65 Davies Street, London W1Y 2AA, UK

11–13 March 1990
2nd Surgical Masterclass of the Royal College of Surgeons of Edinburgh
Aviemore, UK
Information. Mrs Maureen Webb, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

15–18 March 1990
2nd World Congress of Surgical Endoscopy, Ultrasound and Interventional Techniques
Atlanta, Georgia, USA
Information: Program Committee, SAGES, World Congress on Surgical Endoscopy, Suite 409, 1271 Stoner Ave, Los Angeles, CA 90025, USA

19–29 March 1990
Advances in Neurosurgery
Glasgow & Edinburgh, UK
Information: Courses Department, The British Council, 65 Davies St, London W1Y 2AA

28–30 March 1990
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Cardiff, UK
Information The Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

1–6 April 1990
Clinical Genetics
Cardiff, UK
Information: British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

2–12 April 1990
The Clinical Medicine of Later Life: the Scientific Basis of Practice
Oxford, UK
Information: The British Council Courses Dept, 65 Davies Street, London W1Y 2AA, UK

27–28 April 1990
The 3rd International Symposium on Gynaecological Endoscopy
Oxford, UK
Information: Metaphor Conferences & Meetings, 21 Kirklees Close, Farsley, Pudsey, West Yorkshire LS28 5TF, UK

2–4 May 1990
17th Biennial Congress of the Association of Surgeons of South Africa in Bloemfontein
Bloemfontein South Africa
Information: DrGF Ferreira Dept of Surgery, (G72) Univ. of the OFS, Box 339, Bloemfontein 9300, Republic of South Africa

9–12 May 1990
3rd International Symposium on Echocardiography and Doppler in Cardiac Surgery
Vienna, Austria
Information: W. Mohl, c/o Interconvention, A-1450 Vienna, Austria, +43/1/23 69/2642

29 May–1 June 1990
Peripheral Vascular Disease
London, UK
Information: The British Council, Courses Department, 65 Davies St, London W1Y 2AA

5–9 June 1990
European Association for Gastroenterology & Endoscopy: European Digestive Disease Week
Vienna, Austria
Information. Mondial Congress, Faulmanngasse 4/11 A-1040 Wien, Austria

8–9 June 1990
3rd Annual Meeting of The Surgical Infection Society
Antwerp, Belgium
Information: Professor A. Hubens, University Dept of Surgery, Stuivenberg General Hospital, Lange Beeldekenstraat 267, B-2008 Antwerp, Belgium

11–14 June 1990
6th International Congress on Breast Diseases
Boston, Massachusetts, USA
Information: 6th International Congress Secretariat, c/o Office of Continuing Education, Tufts University School of Medicine, 136 Harrison Avenue, Box 36, Boston, MA 02111, USA

13–16 June 1990
5th European Symposium on Gastrointestinal Motility
Augsburg, FRG
Information. Professor M. Weinbeck, Dept. of Internal Medicine III, Zentralklinikum, D-8900 Augsburg, FRG

20–23 June 1990
Annual Meeting of The Endocrine Society
Atlanta, Georgia, USA
Information: Ann singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

22–24 August 1990
International Hepato-Biliary Pancreatic Assoc. 12th Annual Meeting
Hong Kong
Information: The Secretariat, IHBPA Hong Kong, Department of Surgery, Queen Mary Hospital, Hong Kong

15–21 July 1990
1990 Surgical Updating
Milan, Italy
Information. Segreteria Organizzativa, MGR, Via Servio Tullio, 4-20123 Milano, Italy

14–15 July 1990
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

24–28 June 1990
XIII Biennial Meeting of I.S.U.C.R.S.
Graz, Australia
Information: Miss D. Strauss, Executive Secretariat, c/o Indru T Khubchandani, 1275 S. Cedar Crest Boulevard, Allentown, PA 18103, USA

24–29 June 1990
The 3rd Oxbridge Organ Transplantation Course
Oxford, UK
Information: British Council Office, Courses Department, 65 Davies St, London W1Y 2AA

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